

**An Analysis of the Impact of Generic Medicine
Reference Pricing in a Sector of the South African
Private Healthcare Insurance Industry**



by

Jenni Noble-Lückhoff

Student number: NBLJEN001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In partial fulfilment of the requirements for the degree:

Master in Public Health (Health Economics)

Mini-dissertation

February 2015

Supervisor: Professor Diane McIntyre

Health Economics Unit

University of Cape Town

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

Declaration

I, Jenni Noble-Lückhoff, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature:

Signed by candidate

Date: 10 February 2015

Abstract

Background

Pharmaceuticals are responsible for a substantial percentage of the total cost of health care and continue to exceed economic growth and inflation. Generic medicines play an important role in limiting this expenditure, and consequently there is an international drive to implement pro-generic policies particularly in high income countries. One such policy is generic medicine reference pricing (GRP). Generic reference pricing sets a fixed maximum reimbursement amount for clusters of bio-equivalent drugs without placing any restrictions on the manufacturers' price.

Numerous studies have been conducted in high income countries to analyse the impact of generic reference pricing; however, the impact of this reference pricing in low-to-middle income countries (LMICs) is not well established.

Objective

This dissertation aims to address this lack of information in LMICs by providing empirical aggregated claims data on the impact of generic reference pricing on price, expenditure, utilisation and out-of-pocket (OOP) payments in a sector of South Africa's private health insurance industry.

Methods

This time series intervention study of retrospective claim-level secondary data analyses the impact of one of several generic reference pricing models applied by various private medical insurance companies in South Africa. Criteria applied for the selection of referenced categories and sample claims data intend to maximize the data set as well as the analysis period, while minimizing confounders such as medical insurance member variation and specific managed care policies. The impact of the reference price on variables of drug price, drug expenditure, market share and out-of-pocket payment is measured by analysing changes in the originator, 'authorised generic' ('clone') and generic drugs within each cluster. (An 'authorised generic' (AG) is an exact copy of the originator, approved as a brand-name drug under a patent protection but marketed as a generic.)

Results

Two referenced priced categories (Desloratadine and Clopidogrel) and a population of approximately 100,000 were identified as being eligible for inclusion. An authorised generic was launched for Clopidogrel but not for Desloratadine.

The implementation of generic reference pricing appears to have had no or minimal impact on the price of the originator and authorised generic – at the end of the study period the price of the originator drugs of the two categories was 268% and 86% higher than the reference and the authorised generic of Clopidogrel was 69% higher than the reference price. Most often the reference price appeared to be based on the price of a generic drug; however once the reference price was set other generics tended to align at or below the reference price.

The implementation of generic reference pricing was associated with an overall increase in dispensed volumes and a decrease in expenditure for both categories; both categories' originator market share declined dramatically by volume (to 23% and 4%) and value (to 35% and 9%). For Clopidogrel the authorised generic took the majority of market share (63% by volume and 68% by value); the generics only gained one third of the market, despite lower product prices and minimal co-payments. Desloratadine generics captured 80% of the market by the end of the study.

For both categories there was no notable change in the total drug expenditure paid out-of-pocket across the study period. The percentage of drugs dispensed that had a co-payment decreased dramatically for Desloratadine, but were only seen to decrease marginally for Clopidogrel.

Limitations

Due to the small sample and limited reference categories analysed, the findings from this study are not representative of the South African private healthcare sector and cannot be extrapolated to South Africa. In addition, any savings identified should take the expense of non-referenced alternatives into account.

Conclusion

Despite the small sample size, the findings of this study are mostly consistent with literature published on the impact of GRP in high-income countries. In addition, the findings suggest the negative impact that originator manufacturers' marketing strategies have on pro-generic policies by targeting provider brand-loyalty and information asymmetry. This highlights the importance of addressing both supply and demand measures in implementing pro-generic policies. In particular demand measures should be actively pursued to align incentives across the prescriber, dispenser and consumer chain.

Policy Implications

To address the issue of brand-loyalty and the impact of authorised generic marketing strategies, it is proposed that mandatory prescribing by International Non-proprietary Names (INN) in private and public sectors is enforced, as proposed in the National Drug Policy of 1996. This should be implemented in conjunction with improved education on generic prescribing and active promotion of generic acceptance by prescribers and dispensers of medicine, patients and the community as a whole.

Acknowledgements

Professor Diane McIntyre of the Health Economics Unit, University of Cape Town supervised the development of this dissertation and its various components. She provided guidance on the processes, the topic, protocol and its submission, research methodology and data analysis, literature review, journal article, policy brief and manuscript development. She supported and encouraged me tirelessly throughout a rather long process of juggling other priorities with my studies.

Lourens Wepener of Medscheme Holdings Pty (Ltd) assisted me with data management and data analysis.

Yvette van der Westhuizen of MediKredit Integrated Healthcare Solutions assisted with data extraction and collation.

Krish Pather and Thealdi Mitchell of MediKredit assisted me with information on MMAP, MediKredit's generic reference pricing model as well as data extracts of product information and pricing.

Alex Brownlee and Andrew Wright of Medscheme Holdings Pty (Ltd). Alex assisted with data analysis and Andrew enabled this dissertation by giving me study leave to get the work done.

MediKredit Healthcare Solutions (Pty) Ltd permitted and provided access to data and relevant information on their generic reference pricing models. MediKredit also funded 2 years of my MPH studies.

Medscheme Holdings Pty (Ltd) funded 1 year of my studies, and allowed me access to actuarial and statistician resources to assist me.

Abbreviations and terminology

ATC	Anatomic Therapeutic Classification. This is a system of classification for drugs which is controlled by the World Health Organisation Collaborating Centre for Drug Statistics Methodology (WHOC). ¹
Auto-generic / Clone / Copy / Authorised generic / AG	A 'generic' drug that is an exact copy of the originator. It is approved as a brand-name drug under a patent protection but marketed as a generic. It is manufactured either by the originator company or in accordance with the originator company's specifications ¹ . Typically these products are launched just prior to the originator product going off-patent in an attempt to capture market share.
Branded/ Brand-name/Originator product	A medication sold by a pharmaceutical company under a trademark-protected name. Brand-name medications can only be produced and sold by the company that holds the patent for the drug.
CMS	Council for Medical Schemes, South Africa. This is a statutory body which regulates Medical Schemes (medical insurers) in South Africa.
Co-payment	An out-of-pocket payment that is part of the healthcare service cost typically paid at the point of service.
DDD	Defined Daily Dose. The World Health Organisation (WHO) defines the DDD as 'the assumed average maintenance dose per day for a drug used for its main indication in adults' ² .
Dispensing fee	This is the professional practice fee that a pharmacist or dispensing doctor may receive for filling prescriptions. It includes professional services such as patient counselling, monitoring of drug therapy, providing drug information to physicians and dispensing drug products.
DoH	Department of Health, South Africa.
DSP	Designated service provider: a health care provider or group of providers selected by the medical insurer as the preferred provider or providers to provide to its members' diagnosis, treatment and care in respect of one or more prescribed minimum benefit conditions.
External reference pricing / International benchmarking	External reference pricing or international benchmarking is defined as "the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the

¹ Federal Trade Commission, 2011. *Authorised Generic Drugs: Short-Term Effects and Long-Term Impact*. Available from: <http://www.ftc.gov/os/2011/08/2011genericdrugreport.pdf>

² World Health Organisation, 2014. *ATC/DDD Index*. Available from: http://www.whocc.no/atc_ddd_index/

purposes of setting or negotiating the price of the product in a given country”³

Generic drug	The Food and Drug Administration (FDA, USA) defines a generic drug as “A drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use”. The Department of Health refers to a generic as an ‘interchangeable multi-source medicine’.
GRP	Generic Reference Pricing. This refers to a maximum reimbursement level for a defined cluster of drugs. Drugs within the cluster typically have the same active ingredient and pharmaceutical form. Generic reference pricing is also referred to as molecular reference pricing.
HAI	Health Action International. This is a non-profit organisation that represents the interests of consumers in drug policy.
INN	International Non-proprietary Names (INN). The INN is a nomenclature system used to identify active ingredients of medicines. The WHO designates a non-proprietary or generic name to pharmaceutical substances, which is globally recognized. As the INN is unique and distinct this nomenclature enables the identification of pharmaceuticals and avoids confusion in prescribing ⁴ .
LMIC	Low and/or Middle Income Countries
MediKredit	MediKredit Integrated Healthcare Solutions (Pty) Ltd. This is a South African pharmaceutical benefit management company that processes claims for pharmacies, doctors and hospitals.
‘Me-too’ / Incremental innovation drugs / Second generation products/ Follow-up products	These are drugs that are reformulations of existing drugs in dose and/or form or drugs with a new chemical structure for treatment of a disease that already exists ⁵ , and result from ‘follow-up’ research and development.
MMAP	Maximum Medical Aid Price, a generic reference pricing model. MediKredit Integrated Healthcare Solutions (“MediKredit”), a South African Pharmacy Benefit Management company, is the custodian of this model.
MPL	Medscheme Price List, a generic reference pricing model managed by Medscheme Holdings, a medical insurance administrator.

³ Leopold, C., Mantel-Teeuwisse, A.K., Seyfang, L., Vogler S., de Joncheere, K., Laing, R.L., Leufkens, H. 2012, “Impact of External Price Referencing on Medicine Prices – A Price Comparison Among 14 European Countries”, *South Med Review*, vol. 5, no. 2, pp. 34–41

⁴ World Health Organisation, 2014. International Nonproprietary Names. Available from: <http://www.who.int/medicines/services/inn/en/>

⁵ Organisation for Economic Co-operation and Development, 2008. *Pharmaceutical Pricing Policies in a Global Market*. Health Policy Studies. OECD.

NAPPI	National Pharmaceutical Product Index. This is a code that is allocated to all medicines and surgical consumables in South Africa. For medicines it is unique to a product's name, ingredient and salt, dosage form and strength.
NHI	National Health Insurance.
OECD	Organisation for Economic Co-operation and Development: 'a unique forum where the governments of 30 democracies work together to address the economic, social and environmental challenges of globalization' ⁴ .
OOP payment	Out-of-Pocket Payment: Fee paid by the consumer of health services directly to the provider at the time of delivery.
PBM	Pharmaceutical Benefit Manager.
PMB	Prescribed Minimum Benefit(s): a benefit/set of benefits for which a medical insurer must pay in full the diagnosis, treatment and care costs. Co-payments and deductibles are not permitted unless a non-DSP provider has been used or the patient has voluntarily claimed outside of the insurer's treatment protocols and/or formulary.
RP/IRP	Reference price (pharmaceutical)/Internal reference pricing. In the context of this dissertation reference pricing refers to internal reference pricing (IRP) and not external reference pricing (international benchmarking). IRP refers to a maximum reimbursement level for a defined cluster of drugs.
SEP	Single Exit Price. This is the price, approved by the Department of Health, that the manufacturer or importer of a medicine sets. It includes any logistics fees and value-added tax but excludes any dispensing fee.
TRP	Therapeutic Reference Pricing. A maximum reimbursement level applies to a defined cluster of drugs that may be pharmacologically or therapeutically similar.
TRIPS	Trade-Related Aspects of Intellectual Property Rights. TRIPS is an international agreement which has established intellectual property standards for the international trading system. It is administered by the World Trade Organisation (WTO).
VAT	Value added tax. Current value in South Africa is 14%
WHO	World Health Organisation

Reference Methodology

I have used the Harvard style of referencing for all parts of this dissertation, with the exception of the Journal Manuscript. Vancouver reference style is used in the manuscript in accordance with the Instructions for Authors of Health Policy, the peer reviewed journal that I have selected.

I have used Refworks as a reference system. I have noted that there are some variations in Refworks application of citations and bibliography when compared to available guidelines to Harvard referencing. As Refworks is a recommended University of Cape Town reference system I have not changed their application of the Harvard reference system.

Contents

PART A: PROTOCOL	A-1
Introduction	A-3
Problem statement and justification for research	A-3
The South African context	A-4
Literature review	A-6
Definitions.....	A-6
Objectives of reference pricing.....	A-7
International status of generic reference pricing	A-7
The effects of generic reference pricing	A-8
Aim and objectives	A-9
Methodology.....	A-10
Study design and measurements	A-10
Sampling strategy	A-10
Characteristics of the study population.....	A-12
Instruments.....	A-12
Analysis.....	A-14
Data management	A-14
Data analysis	A-15
Ethics and communication.....	A-16
Ethics.....	A-16
Stakeholders	A-17
Reporting	A-17
Logistics	A-18
Risks.....	A-18
References	A-19
PART B: STRUCTURED LITERATURE REVIEW	B-1
Objective.....	B-2
Search strategy and selection criteria	B-2
Introduction	B-4
Pro-generic pharmaceutical policies	B-5
Supply side policies	B-7
Demand-side policies.....	B-7
Determinants and Impact of Generic Market Entry and Penetration.....	B-10
Marketing Strategies.....	B-12
Reference pricing	B-18
Definition	B-18
Reference Pricing Objectives	B-19
Types of Reference pricing	B-20
Country analysis.....	B-22
The impact of GRP	B-26
Effect on Product Price	B-27
Effect on Drug Utilisation and Market Share.....	B-30
Effect on Expenditure	B-31

Impact on Out of Pocket (OOP) Payments	B-32
Impact on Health Outcomes	B-32
Identification of gaps / Needs for further research	B-33
References	B-35
PART C: JOURNAL MANUSCRIPT	C-1
Abstract	C-3
Highlights	C-4
Key words	C-4
Introduction	C-5
Methods	C-7
<i>Study design</i>	<i>C-7</i>
<i>Sampling strategy</i>	<i>C-7</i>
<i>Outcomes measured</i>	<i>C-8</i>
<i>Data analysis</i>	<i>C-8</i>
Results	C-9
<i>Sample population and GRP categories</i>	<i>C-9</i>
<i>Impact on price</i>	<i>C-9</i>
<i>Impact on expenditure, volumes and market share</i>	<i>C-11</i>
<i>Impact on out-of-pocket payments</i>	<i>C-15</i>
Discussion	C-17
<i>Limitations</i>	<i>C-20</i>
Conclusion	C-21
References	C-22
Online Appendix	C-24
PART D: POLICY BRIEF	D-1
PART E: APPENDICES	E-1
Appendix A: List of Data Fields required per GRP Category	E-2
Appendix B: List of Data Fields Required for Claims from MediKredit	E-2
Appendix C: List of Data Fields required for All Products mapping to Sample MMAP Categories	E-3
Appendix D: Ethics Approval Letter	E-4
Appendix E: Journal instruction to authors	E-5

List of tables

Table 1: Generic pharmaceutical policies	B-6
Table 2: Impact of expiry of originator brand patent and generic entry	B-12
Table 3: Legislated Single Exit Price increases	B-16
Table 4: Generic reference pricing models in South Africa's private healthcare insurance market.....	B-17
Table 5: Comparison of different levels/phases of reference pricing	B-20
Table 6: Country Analysis of Reference Pricing Models.....	B-24

List of figures

Figure 1: Impact of GRP on prices of Clopidogrel and Desloratadine products over the study period.....	C-11
Figure 2: Impact of GRP on Clopidogrel products over the study period	C-13
Figure 3: Impact of GRP on Desloratadine products over the study period	C-15
Figure 4: Impact of GRP on out-of-pocket payments	C-17

Part A: Protocol

Contact details

Masters Candidate

(Investigator)

Jenni Noble, MBChB

4 Fern Close

Constantia, Cape Town, 7806

jennin@medscheme.co.za

+27 (0)83 443 1110 (phone)

Supervisor

Di McIntyre, BCom MA PhD

Professor

Health Economics Unit

School of Public Health and Family

Medicine

University of Cape Town

Faculty of Health Sciences

Anzio Rd, Observatory

Diane.McIntyre@uct.ac.za

+27 (0)21 406 6579 (phone)

Introduction

Pharmaceuticals are responsible for a substantial percentage of the total cost of health care. Fuelled by the characteristics of market imperfection and the relatively inelastic demand for medicines, the increase in pharmaceutical expenditure continues to exceed economic growth and inflation (Organisation for Economic Co-operation and Development (OECD) 2008).

Against this background many countries have implemented pharmaceutical pricing policies to control costs. These policies target different components of the price chain including the manufacturer, the wholesaler and the retailer's price (Aaserud et al. 2006). Examples of such policies include price caps, negotiated prices, price freezes, international benchmarking (also referred to as external reference pricing), profit regulation, index pricing and reference pricing (RP) (Aaserud et al. 2006). Frequently various combinations of these policies are implemented.

Internal reference pricing (IRP) refers to a maximum reimbursement level for a defined cluster of drugs. Typically a patient will pay the difference between the price of the dispensed drug and the reference price. Different models of internal reference pricing exist. These are largely defined by the criteria for inclusion within a cluster. In generic reference pricing (GRP) models, also referred to as molecular reference pricing, drugs within the cluster typically have the same active ingredient and pharmaceutical form. Therapeutic reference pricing (TRP) clusters may be pharmacologically or therapeutically similar.

Internal reference pricing (as opposed to external reference pricing) is referred to as 'reference pricing' in this dissertation.

Problem statement and justification for research

Many countries have implemented GRP models at a national or individual insurance scheme level. This is particularly true for the Organisation for Economic Co-operation and Development states (OECD 2008). However, concerns have been raised on the mixed effects of GRP in particular on its impact on drug pricing competition, utilisation patterns, health outcomes, innovative drug development and equity issues related to out-of-pocket (OOP) payments ('a fee paid by the consumer of health services directly to the provider at the time of delivery' (World Health Organisation 2000)). In addition GRP has been shown to result in

short-term cost-savings. In order to maintain savings over longer periods of time it becomes necessary to implement reference pricing for additional clusters of drugs (Golob, Molj & Podnar 2007).

Despite these concerns, historically there are few published studies of the empirical effect of reference pricing (López-Casasnovas, Puig-Junoy 2000). In the past 10 years publications have increased in OECD countries, but in low and/or middle-income countries (LMIC) there remains a paucity of published research on the impact of pharmaceutical policies to increase the use of generics, including GRP, both at national and private insurer level (Faden et al. 2011, Kaplan et al. 2012). In a meta-analysis of published literature from 2000 to 2010, Kaplan et al referenced only one article on generic reference pricing in LMICs. In their conclusion they stressed that ‘Evaluations of generic medicines policies in LMICs are urgently needed’ (Kaplan et al. 2012, p. 223). Most available empirical studies address the impact of reference pricing on product prices; studies assessing the impact of RP on utilisation and expenditure are frequently not as robust as price studies. In addition many studies use aggregate level rather than individual case/patient-level data, due to the lack of accessibility to micro-data.

This dissertation aims to address this dearth of information by providing robust empirical data, based on individual case data, on the impact of GRP on price, utilisation, expenditure and OOP payments in South Africa’s private health insurance industry.

The research findings will provide useful evidence to assist in developing optimal GRP policies, specifically in LMICs.

The South African context

South Africa has a fragmented, two tier healthcare system. 8.76 million people (approximately 16% of total population) have private medical insurance (Council for Medical Schemes 2014), and the remaining 84% of the population use the public sector and/or private sector, the latter being on an out-of-pocket (OOP) basis. The privately insured market however uses 43% (R84.7 billion) of the country’s total healthcare spend. 17% (R14 billion) of this private insurance healthcare expenditure is spent on medicines, excluding hospital medicines. Significant increases in medical insurers’ expenditure, particularly on medicines, were especially apparent from the mid-’80s to mid-90’s (Council for Medical Schemes 2011).

In the past decade several regulatory interventions and policies have been implemented in an effort to control medicine prices in the private sector, including limited pro-generic policies. The Department of Health (DoH) has indicated that the aim of the regulatory interventions is to “Protect the South African health system from paying distorted prices for medicines through the elimination of price distortions and price distorting behavior” (Department of Health 2010). Regulations and policies relating to medicine pricing that have been implemented include regulation of the price of medicines and dispensing fees, the prohibition of rebates, discounts and other incentive schemes offered by manufacturers to providers and mandatory generic substitution. Draft regulations includes international benchmarking of prices of medicines (external reference pricing), regulation of logistic fees that manufacturers pay for the distribution of medicines and pharmacoeconomic evaluation requirements for new chemical entity medicines and for new indications for existing medicines. In addition all scheduled medicine must be registered by South Africa’s Medicine Controls Council (MCC) prior to marketing the product in South Africa. Any ‘interchangeable multi-source medicine’ (generic) must prove bioequivalence to the originator to get registration approval. Further detail on these policies and regulations is provided in the literature review section of this dissertation.

There is no national GRP system in South Africa, but GRP and TRP are applied by various medical insurers in the private insurance industry, sometimes simultaneously. The first GRP model called “Maximum Medical Aid Price” (MMAP) was implemented in 1987 by MediKredit Pty (Ltd). MMAP clusters include interchangeable multi-source products that have exactly the same active ingredient/s and salt/s combination, strength of the active ingredient/s and dosage form (for example tablets versus capsules) as other pharmaceutical products. Products are excluded from the MMAP listing if substitutability data from international sources indicate concerns of substitution in drugs with narrow therapeutic index in life-threatening diseases. MMAP categories and prices are typically updated annually but ad hoc updates are also made in accordance with price changes of pharmaceutical products within an existing category, the launch of new pharmaceutical products that prompt the creation of new categories and the discontinuation of pharmaceutical products and/or withdrawal of pharmaceutical products within an existing category requiring the deletion of the category. Prices are determined to allow flexibility when selecting a pharmaceutical product.

Subsequently multiple GRP models based on different methodologies have been implemented by different medical insurer administrators and pharmacy benefit managers (author's own industry knowledge). The complexity of the variety and variability of GRP models impacts prescribers and dispensers and is thought to dilute the intended impact of the individual GRP models.

Pharmaceutical marketing practices used internationally to protect the market share of originators by minimizing or delaying the entry and penetration of generics, are common in South Africa. These include the launch of 'me-too' products (also referred to as 'second generation', 'follow-up' and 'incremental innovation' drugs) which are reformulations of existing drugs resulting from follow-up research and development as well as 'authorised generics', also known as 'clones' and 'auto-generics' (Federal Trade Commission 2011). Authorised generics (AGs) are manufactured either by the originator company or by another pharmaceutical manufacturer through acquisition or joint venture. They may be launched prior to the originator's patent expiry in an effort to gain the 'first-mover advantage' in which the first generic launched is able to gain substantial market share at a higher price than that of later generics (López-Casasnovas, Puig-Junoy 2000).

Literature review

Definitions

Reference pricing is a mechanism used to control pharmaceutical expenditure. External reference pricing refers "the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country" (Leopold et al, 2012). Internal reference pricing is a method of reimbursement. The maximum price that a third party payer will reimburse a specific drug is defined by its internal reference price for that drug's cluster. Typically an OOP payment equivalent to the difference between the dispensed medication and the reference price is due by the consumer if the price of the dispensed drug is higher than the reference price (Miraldo 2009, Galizzi, Ghislandi & Miraldo 2011). This OOP payment is often referred to as cost-sharing (Aaserud et al. 2006).

The equivalence criteria of the cluster determine the type of internal reference pricing. Three basic types of clustering are defined based on chemical, pharmacological or therapeutic equivalence. In GRP chemical equivalence criteria are applied. Included products typically have the same active ingredient, strength and dosage form as an off-patent originator drug and are generally considered interchangeable (Aaserud et al. 2006, Galizzi, Ghislandi & Miraldo 2011). Therapeutic reference pricing (TRP) may include clusters of drugs that are chemically different but pharmacologically similar with similar or identical indications; or the clusters can be therapeutically similar and include all drugs to treat a specific condition (Aaserud et al. 2006, Galizzi, Ghislandi & Miraldo 2011). Reference pricing is often applied in combination with other policies aimed to control pharmaceutical expenditure such as price capping, controlling pharmacists' margins and mandatory generic substitution.

Objectives of reference pricing

The ultimate objective of reference pricing is control of pharmaceutical expenditure with no associated negative health outcomes (López-Casasnovas, Puig-Junoy 2000) and no discriminatory effects (Miraldo 2009). Its effectiveness depends on its ability to influence both the supply- and demand-side of pharmaceuticals. Demand control aims to limit the quantity of medicine dispensed. Supply is controlled by creating price competition around the reference price resulting in an attempt to “induce price responses from the pharmaceutical firms” (Brekke, Konigbauer & Straume 2007) to ensure that market share is not lost (López-Casasnovas, Puig-Junoy 2000, Aaserud et al. 2006). The success of reference pricing is influenced by multiple factors. These are detailed in the substantive literature review section of the dissertation.

International status of generic reference pricing

GRP is a common pharmaceutical policy in many countries. In Europe the majority of countries apply some form of officially set reference pricing. Most use chemical equivalence as the criteria for reference pricing, but some countries apply varying combinations of TRP and GRP (Puig-Junoy 2010). LMICs mostly apply national generic substitution policies, but few of these countries currently apply GRP. Where it is applied, there is very little literature available on its effects. As indicated above there are several models of GRP that are applied in South Africa's private healthcare sector.

Across all countries the RP models differ considerably in terms of equivalence criteria and price calculation.

The effects of generic reference pricing

The jury is still out on the long-term effectiveness and clinical outcomes of GRP. This speculation is fuelled by the lack of available long-term data (Golob, Molj & Podnar 2007).

Effect on product price

Theoretical studies predict that with the implementation of RP, drugs that are priced higher than the reference price will decrease in price, and the quantum of this decrease depends on the design of the RP model, the number of drugs in a cluster, consumer price sensitivity and consumer perception of the substitutability of generics for brand-name drugs. In addition theory suggests that the price of non-referenced therapeutic alternatives may increase (Brekke, Holmas & Straume 2011).

Several empirical studies were found to support these theoretical predictions (Puig-Junoy 2010, Galizzi, Ghislandi & Miraldo 2011). Puig-Junoy reported that price decrease often occurred rapidly after GRP implementation, but these decreases were however asymmetrical (Puig-Junoy 2010). A Slovenian study however partially supported the 'generic paradox' (López-Casasnovas, Puig-Junoy 2000) theory as the prices of several original products did not decrease with the launch of generic products and the implementation of reference pricing (Golob, Molj & Podnar 2007).

The decrease in price due to GRP is generally much smaller than that of TRP models, which supports theoretical predictions (Galizzi, Ghislandi & Miraldo 2011). In addition, price drops have been positively correlated with the number of generic categories (Puig-Junoy 2010).

A study by the European Commission (European Commission 2009) showed that price reductions were greater when GRP is combined with mandatory generic substitution and when reference prices are regularly revised.

Effect on expenditure and utilisation

The introduction of RP (GRP and TRP) is predicted to impact the utilisation and market share of originator and generic drugs (Miraldo 2009). Generic market share increases significantly if originator products do not drop their prices to RP levels (Ghislandi, Krulichova & Garattini 2005, Golob, Molj & Podnar 2007, Galizzi, Ghislandi & Miraldo 2011). In addition empirical studies in multiple countries have shown a significant reduction in total expenditure. This decrease is reported to be most significant in the short-term (Simoens et al. 2005, Ghislandi, Krulichova & Garattini 2005, Puig-Junoy 2007).

Impact on out-of-pocket (OOP) payments

OOP payments resulting from cost-sharing policies have been shown to reduce demand (Fiorio, Siciliani 2010). However, providers frequently determine demand. As such a prescriber's reluctance to use generics together with information asymmetry may result in increased GRP OOP payments. This may reduce equity in healthcare as cost-shifting could be directed to individuals who may not be able to cost-share (Mossialos, Mrazek & Walley 2004).

Aim and objectives

The aim of this study is to investigate the impact of generic medicine reference pricing and thereby contribute to generic medicine pharmaceutical pricing policies and their implementation, particularly in LMICs.

The specific objective is to analyse the impact of the implementation of new generic reference pricing categories in part of the South African private sector on:

- The price of drugs subject to GRP;
- The expenditure and utilisation of drugs subject to GRP;
- Market share dynamics;
- Patient out-of-pocket (OOP) payments.

This study does not include consideration of therapeutic reference pricing (TRP), the effect of GRP on drugs not subject to GRP, the impact on pharmaceutical innovation and health

outcomes, and the impact of GRP on overall healthcare utilisation, i.e. hospitalization, doctor and overall medicine expenditure.

Methodology

Study design and measurements

This is a quasi-experimental study. The study design is an analysis of a natural experiment. It is an intervention study using retrospective patient-level (not aggregated) secondary data obtained through records review.

Sampling strategy

MediKredit's 'Maximum Medical Aid Price' (MMAP) model is the GRP model that is evaluated as an intervention. MMAP has been selected for two reasons: as the first GRP model in South Africa it has been the industry standard since 1987, and, as the author worked for MediKredit at the time of initiating this research, access to the data was facilitated.

MMAP categories were selected based on the following selection criteria: (i) categories should have comparatively high volumes to ensure that the most significant drug categories based on market share are reviewed; (ii) categories should have been newly implemented between April 2008 and July 2009, for the following reasons:

- to minimize confounding that would occur due to the implementation of mandatory generic substitution in 2003 and medicine price regulation (Single Exit Price - SEP) in 2004; and
- because data prior to 2008 is not available;
- to enable a post-implementation analysis period of at least 4 years; and
- to maximize the sample size.

The first step was to identify eligible MMAP categories, in accordance with criteria defined above. A list of all MMAP categories that were implemented between 1 April 2008 and 31 July 2009 was obtained from the MediKredit database. Exclusion criteria included the following:

- Categories implemented prior to 1 April 2008 due to issues of data availability.

- Categories implemented after 31 July 2009 were also excluded to ensure that the MMAP category had been effective for at least 3 years and to maximize the data set.
- Any category that was withdrawn either temporarily or permanently during this period
- Any category to which therapeutic reference pricing applied, as the TRP is in some cases lower than the GRP and will act as a confounder.

Next, the list of MMAP categories identified were analysed against the claims database to establish which categories had the greatest volumes. A list of all products per identified MMAP category was then requested from MediKredit, together with a flag indicating whether each product is an original, generic or AG. MediKredit, as the custodian of the National Pharmaceutical Product Index (NAPPI) codes, produces and distributes a product file throughout the industry. This file is updated daily with new products and SEP changes that have been approved by the Department of Health.

The third step was to obtain the price history for each MMAP category as well as for each drug over the defined period. Data required for each MMAP category is detailed in Appendix A in Part E.

The fourth step in the sampling strategy was to identify eligible medical insurers that applied MMAP consistently over the analysis period. In an effort to minimise confounders, insurers were excluded if the following applied:

- a customised variation of GRP was applied. In the MediKredit environment some insurers opted to customise the reference price and/or the frequency of review;
- membership varied by more than 20% over the study period;
- closed formularies were applied which limited access to equivalent drugs in the GRP category;
- benefit exclusions for some or all of the identified MMAP categories applied.

Finally the claims data to be analysed was extracted. In addition to identifying only those claims that are impacted by the sample MMAP categories and corresponding drugs, the following inclusion and exclusion criteria were applied:

- Include claims with a processing date from 4 months prior to the applicable MMAP category implementation to at least 4 years after MMAP category implementation to allow for appropriate periods for the before and after analyses. Where claims data is available for longer than 4 years this should be included.
- Include a medical insurer's data (non-identifiable) only if MMAP was applied throughout the period of analysis and the medical insurer's membership did not vary by more than 20% over the period of analysis. This criterion is necessary as any major change in membership numbers and associated change in member profile could introduce confounding.
- Include approved claims only (not rejected or reversed claims).

Pricing data should exclude dispensing fees as these may vary across schemes and providers and will introduce an element of confounding.

Characteristics of the study population

The sample claims data analysed was for patients of any age that were members of private health insurers that processed all of their medicine claims through MediKredit.

Instruments

MediKredit's data warehouse was used to obtain claims data for analysis. Claims data was requested for products that are specific to the identified sample of GRP categories, based on defined data entry criteria. Data did *not* include any patient-identifiable indicators such as name, medical insurance membership number or date of birth. The claims data did *not* include any provider, medical insurer and/or medical administrator-identifiable indicators. The data fields required per claim are listed in Appendix B in Part E.

Outcomes

The impact of the implementation of each of the identified MMAP categories has been measured for several variables. In each case the impact of MMAP on the sample is measured by analyzing changes to the originator, AG (where applicable), generics and overall MMAP category (across all drugs in cluster).

The changes in the variables are measured from one time interval to another. The time intervals are referred to as 'periods'. These 'periods' are the 4 months prior to the implementation of MMAP (MMAP launch date), the time interval after MMAP launch, and the periods between subsequent MMAP price changes.

The first variable is the impact of GRP on the price of products in the reference pricing cluster. The second and third variables are drug expenditure and quantity dispensed. The fourth and fifth variables are the percentage of the market share, based on both volume and expenditure.

The final variables relate to OOP payments. These variables determine whether MMAP has achieved its objective of encouraging a switch to lower-cost generics in order to reduce OOP payments. This is determined by analysing whether there have been changes in the volumes, expenditure and quantum of OOP payments per referenced category. The percentage of total dispensed volumes that generates an OOP payment, the percentage of total drug expenditure that was paid out-of-pocket and the quantum of the OOP payment (where an OOP payment applies) are measured.

Reliability and validity of measurements/data

The accuracy of MediKredit's medicine product file is ensured through a rigorous process: new medicines, and/or product prices and product terminations are only updated once communicated by the DoH. All changes to the product file are then validated by a Quality Control department. Indicators of the product file such as the acute, chronic and acute/chronic indicators and generic/original flags are assigned based on a set of pre-defined rules to ensure accuracy.

The reliability and validity of MediKredit's claims data is also ensured through a rigorous process, necessitated by the fact that it is used for financial reimbursement. Basic data validation checks are done such as member details, provider and drug code checks; the risk of provider technical error is reduced through the use of validation checks e.g. an inappropriate quantity on a claim due to provider 'finger trouble' when submitting the claim will be rejected based on excessive quantity controls. Most claims are submitted in an on-line real-time environment so providers are immediately notified of errors and can resubmit the claim

immediately. All product prices are checked against an industry price file, which is in line with the DoH SEP file, and are marked down where prices higher than SEP are submitted.

Analysis

Data management

A list of all products falling into the sample was provided by MediKredit, together with relevant fields including a flag indicating whether a product is an original, generic or AG. The drug manufacturer was contacted to confirm AG products. See Appendix C in Part E for detail.

Defined Daily Dose (DDD) values per ATC were obtained from the WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD Index website (World Health Organisation 2014). DDD is defined as ‘the assumed average maintenance dose per day for a drug used for its main indication in adults (World Health Organisation 2014)’. Each MMAP category included in the sample was allocated a DDD. At a claim level the claims data was converted to DDD and cost data converted to cost per DDD.

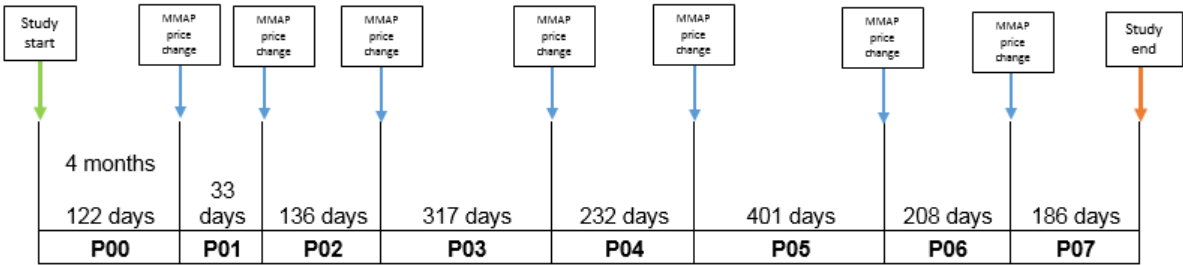
Where a product’s pack size was different to that of the MMAP category, then the price for the product was calculated based on the MMAP pack size. E.g. If the MMAP pack size is 30, but the products pack size and associated price is 28, then the product’s price will be calculated based on a pack size of 30.

Monetary figures are in nominal terms and have not been adjusted for inflation.

As the implementation dates and subsequent price changes of the different reference categories vary, it was necessary to convert the calendar dates to a common denominator. As such the overall length of the study for each reference category was divided into individual time intervals, referred to as ‘periods’ in the study. The first period is the 4 months preceding the implementation of that category’s MMAP, and is referred to as P00. The subsequent periods are the time intervals between each MMAP price change for that category. The period that follows MMAP launch is P01. P02 follows the next change in MMAP price, etc. Within each period the reference price remains fixed but the price of individual drugs within each cluster may change, potentially in response to the MMAP price change. As the total study

duration of each reference category varies and the number of MMAP price changes vary, the number of ‘periods’ per referenced category may differ.

The time interval methodology is illustrated below:



All claims data was then time-adjusted based on the date of implementation of the MMAP category. Each claim was allocated to a specific period in accordance with the MMAP price changes and the date of the claim.

The data for the generic drugs were averaged for each outcome measure to allow a comparison to the originator and AG. For price, a minimum and maximum value was allocated.

As the duration of each time period differs, it was also required to convert the expenditure and dispensed volumes per time period to a daily quantity to ensure that a common denominator of comparison is used i.e. Expenditure per day and number of DDDs per day.

Data analysis

The impact of MMAP on each cluster’s product prices is analysed by comparing the changes in price of the originator, AG and generics (average, minimum and maximum price) relative to the changes in MMAP price over each allocated ‘period’ and across the full study period.

Expenditure is measured by analyzing the average expenditure per day, and the average expenditure per DDD. Drug expenditure is reported ‘per day’ to ensure a comparable denominator as the period intervals between MMAP price changes are not consistent. Expenditure per day is a function of price and utilisation, whereas expenditure per DDD takes into account the variation in product price, while controlling for volume changes.

Dispensed quantity is measured by calculating the number of DDDs dispensed per day. Market share is analysed by volume and value. The change in the dispensed DDDs as a % of total expenditure and as a % of total volume is analysed.

Changes in expenditure, quantities and market share are quantified for the originator, AG and average generic and compared from one 'period' to another as well as across the full study period.

Analysis of OOP payments includes 3 variables:

- The percentage of total dispensed volumes that generate an OOP payment is measured as the number of DDDs with an OOP payment as a % of total DDDs,
- The percentage of total drug expenditure that was paid out-of-pocket is measured as the OOP expenditure as % Total Expenditure
- The quantum of the OOP payment is measured as the OOP value per DDD, where an OOP payment applies.

All of the above results are documented in tabular format for each variable per allocated 'period'. In addition the results are displayed as time-series graphs to depict changes for each of the variables.

Ethics and communication

Ethics

As this research is a retrospective analysis of claims processed for billing purposes and does not involve the use of any identifiable or potentially identifiable patient-, provider-, or medical insurance-specific data it can be considered as being of low ethical risk. In addition data will not be stored for future analysis. However, there are some ethical considerations that need to be taken into account.

Permission to supply and use the product file and claims data was obtained from MediKredit Integrated Healthcare Solutions. As no claims data provided by MediKredit is identifiable for patients, providers or insurers and data is presented at an aggregated level, consent from these parties is not required.

Before proceeding with the study ethical approval was obtained from the Health Sciences Research Ethics Committee, University of Cape Town (See Appendix D in Part E).

Stakeholders

The primary stakeholder in this study is MediKredit. Other stakeholders are the pharmaceutical companies (originator and generic), medical insurers & their members, medical insurance administrators, managed care organisations and pharmacy benefit managers, particularly companies that are custodians of GRP models.

Government and affiliated stakeholders include the Department of Health, Medicines Control Council, Health Professionals Council of South Africa, South African Pharmacy Council and the Council for Medical Schemes.

Industry body stakeholders include the Pharmaceutical Society of South Africa, South African Medical Association (SAMA), Innovative Medicines of South Africa (IMSA) and the National Association of Pharmaceutical Manufacturers. In addition the World Health Organisation and Health Action International, specifically the WHO-HAI Project on Medicine Pricing and Availability, are relevant stakeholders.

Reporting

The primary stakeholders detailed above will be informed of all of the findings of the study. The researcher recognizes her ethical responsibility to use the findings generated in this study to act accordingly. The findings will also be written up in a publicly accessible format, as it is the researcher's specific intention to publish this study, especially considering the lack of empirical GRP data in LMICs.

A policy brief that includes the research findings is included as part of the dissertation. The researcher will attempt to publish this brief and distribute it to relevant stakeholders, including the government and industry stakeholders detailed above and the WHO/HAI project coordinators.

Logistics

MediKredit data is backed up on a daily basis hence the risk of losing this data is minimal. GRP model categories and pricing history data was backed up on a personal external hard drive. The data is captured and stored electronically in a password protected file.

Risks

As there has been no engagement with patients or medical insurers no physical, psychological, social, economic or legal risks apply.

References

- Aaserud, M., Austvoll-Dahlgren, A., Kösters, J.P., Oxman, A.D., Ramsay, C. & Sturm, H. 2006, "Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies", *The Cochrane Library*.
- Brekke, K.R., Konigbauer, I. & Straume, O.R. 2007, "Reference pricing of pharmaceuticals", *Journal of health economics*, vol. 26, pp. 613+.
- Brekke, K.R., Holmas, T.H. & Straume, O.R. 2011, "Reference Pricing, Competition, and Pharmaceutical Expenditures: Theory and Evidence from a Natural Experiment", *Journal of Public Economics*, vol. 95, no. 7-8, pp. 624-638.
- Council for Medical Schemes 2011, *Annual Report 2010-2011*, Council for Medical Schemes.
- Council for Medical Schemes 2014, *Annual Report 2013-2014*, Council for Medical Schemes.
- Crasto, A.M. 2014, , *New drug approvals*. Available: <http://newdrugapprovals.org/south-africa-mcc/> [2014, August 14].
- Department of Health 2010, *Medicines and Related Substances Act, 1965; Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances: (Methodology for International Benchmarking of Prices of Medicines and Scheduled Substances in South Africa)*. Pretoria: Department of Health, Government Gazette 9941.
- European Commission 2009, , *Pharmaceutical Sector Inquiry. Final Report*. Available: <http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/> [2011, September 5].
- Faden, L., Vialle-Valentin, C., Ross-Degnan, D. & Wagner, A. 2011, *WHO/HAI Project on Medicine Prices and Availability. Review Series on Pharmaceutical Pricing Policies and Interventions . Working Paper 2: The Role of Health Insurance in the Cost-Effective Use of Medicines*, Drug Policy Research Group and WHO Collaborating Center in Pharmaceutical Policy. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute.
- Federal Trade Commission 2011, "Authorized generic drugs: short-term effects and long-term impact", *Retrieved September*, vol. 10, pp. 2014.
- Fiorio, C.V. & Siciliani, L. 2010, "Co-payments and the demand for pharmaceuticals: evidence from Italy", *Economic Modelling*, vol. 27, no. 4, pp. 835-841.
- Galizzi, M.M., Ghislandi, S. & Miraldo, M. 2011, "Effects of reference pricing in pharmaceutical markets: a review", *PharmacoEconomics*, vol. 29, no. 1, pp. 17-33.
- Ghislandi, S., Krulichova, I. & Garattini, L. 2005, "Pharmaceutical policy in Italy: towards a structural change?", *Health policy (Amsterdam, Netherlands)*, vol. 72, no. 1, pp. 53-63.

- Golob, U., Molj, B. & Podnar, K. 2007, "How reference pricing for pharmaceuticals can increase generic share of market: the Slovenian experience", *Journal of Public Policy and Marketing*, vol. 26, no. 1, pp. 89+.
- Kaplan, W.A., Ritz, L.S., Vitello, M. & Wirtz, V.J. 2012, "Policies to promote use of generic medicines in low and middle income countries: A review of published literature, 2000-2010", *Health Policy*, vol. 106, no. 3, pp. 211-224.
- Leopold, C., Mantel-Teeuwisse, A.K., Seyfang, L., Vogler S., de Joncheere, K., Laing, R.L., Leufkens, H. 2012, "Impact of External Price Referencing on Medicine Prices – A Price Comparison Among 14 European Countries", *South Med Review*, vol. 5, no. 2, pp. 34–41.
- López-Casasnovas, G. & Puig-Junoy, J. 2000, "Review of the literature on reference pricing", *Health policy*, vol. 54, no. 2, pp. 87-123.
- Miraldo, M. 2009, "Reference pricing and firms' pricing strategies", *Journal of health economics*, vol. 28, no. 1, pp. 176-197.
- Mossialos, E., Mrazek, M. & Walley, T. 2004, *Regulating Pharmaceuticals In Europe: Striving For Efficiency, Equity And Quality: Striving for Efficiency, Equity and Quality*, McGraw-Hill International.
- Organisation for Economic Co-operation and Development (OECD) 2008, *Pharmaceutical Pricing Policies in a Global Market*, OECD Health Policy Studies.
- Puig-Junoy, J. 2007, "The impact of generic reference pricing interventions in the statin market", *Health policy*, vol. 84, pp. 14+.
- Puig-Junoy, J. 2010, "Impact of European pharmaceutical price regulation on generic price competition: a review", *PharmacoEconomics*, vol. 28, no. 8, pp. 649-663.
- Simoens, S., De Bruyn, K., Bogaert, M. & Laekeman, G. 2005, "Pharmaceutical policy regarding generic drugs in Belgium", *PharmacoEconomics*, vol. 23, no. 8, pp. 755-766.
- World Health Organisation 2000, *A Quick Reference Compendium of Selected Key Terms used in The World Health Report 2000 issued by the World Health Organisation*. Available: http://www.who.int/health-systems-performance/docs/glossary.htm#outofpocket_payments [2011, October 9].
- World Health Organisation 2014, *ATC/DDD Index*. Available: http://www.whocc.no/atc_ddd_index/ [2014, September 12].

Part B:

Structured Literature Review

Objective

This literature review aims to provide an introduction to generic medicines, highlighting the cost advantage of increased generic utilisation. An overview is provided of various pro-generic policies, including generic reference pricing (also referred to as molecular reference pricing), illustrating how their effectiveness varies based on the complex and variable combinations that are implemented. Factors impacting generic market penetration are detailed, with specific reference to the 'tool-box' of marketing strategies that are used to promote and restrict the use of generic medicines.

As this dissertation focuses on the impact of generic reference pricing in the private healthcare sector in South Africa, particular reference is made to pro-generic and other pharmaceutical policies in this country.

Finally, I focus on the different types of medicine reference pricing systems, providing an overview of different models of reference pricing and their various applications internationally. In keeping with the objective of my dissertation, key findings from studies that investigate the impact of generic reference pricing (GRP) is provided, including the impact on product price, drug utilisation and market share, overall expenditure and out-of-pocket payments. Although my investigation does not cover the health outcomes impact of generic reference pricing, reference is made to outcomes where data is available.

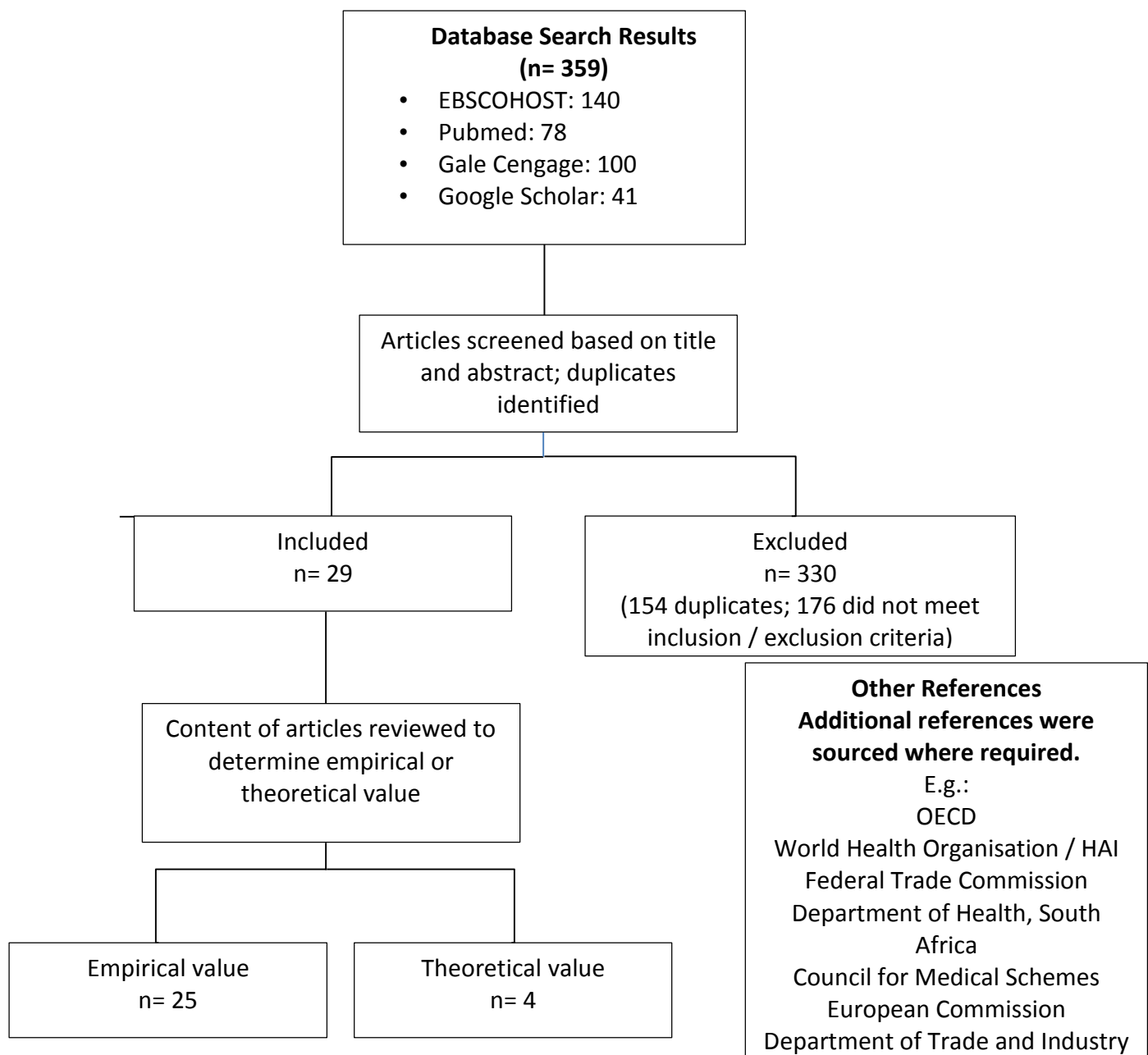
Search strategy and selection criteria

I searched for publications between 1 January 2000 and 30 June 2013 in English. A full text search was conducted. The following databases were searched: EBSCOHOST (Cumulative Index to Nursing and Allied Health Literature (CINAHL), EconLit and Medline); Pubmed; Gale Cengage, Cochrane Library and Google scholar. I assumed that any rigorous studies would most likely be published, and hence limited my search on grey literature to the following websites: WHO/HAI, European Commission and OECD. Where country-specific information, legislative or industry data was required, I searched specific websites, including (but not limited to) the Council for Medical Schemes (South Africa), Department of Health (South Africa), Department of Trade and Industry, European Generic Medicines Association, Federal Trade Commission, Mediscor and Intercontinental Marketing Services (IMS).

Search terms used were (reference price* or index price*) AND (generic or multisource or multi-source or interchangeable) AND (drug or medicine or pharmaceutical). See Figure 1 for an overview of the search strategy and results.

The search strategies intended to capture high-income countries (e.g., United States, Europe, Canada, New Zealand, Australia etc.) and low and middle income countries (LMIC).

Figure 1: Search strategy algorithm



Introduction

Generic medicines are described by the World Health Organisation (WHO) as being pharmaceutical products which are 'intended to be interchangeable with an innovator product', 'manufactured without a licence from the innovator company', and 'marketed after the expiry date of the patent or other exclusive rights.' (World Health Organisation 2014b). The underlying principle of generic medicines is that they should demonstrate bioequivalence to a reference drug which is usually the originator. Generic drugs may be referred to as unbranded, off-patent, or multi-sourced drugs (Mossialos, Mrazek & Walley 2004).

'Authorised generics', 'clones' or 'co-marketed copies' (referred to as AGs in this dissertation) are often referred to as generics; however although they have the same active ingredient, they are marketed under the originator's license under a different name (Dylst, Vulto & Simoens 2011).

The advantage of generic medicines is that they do not require the same research and development as originator drugs. As such there is a price advantage. Intercontinental Marketing Services (IMS) has estimated in their 'Responsible use of Medicines' report that between 19 and 40 billion US dollars could be saved worldwide through increased use of safe, low-cost generics (Intercontinental Marketing Services 2012). The price advantage of generic medicines is also evident in LMIC countries. A 2010 WHO paper reports that price surveys conducted across a basket of medicine purchased in the private sector in 17 LMICs showed that use of the lowest cost generic instead of the originator drug could achieve a cost saving of more than 50% in 15 of the 17 countries surveyed (an average of 9% to 89%) (Cameron, Laing 2010).

Although there is a worldwide trend towards increasing generic utilisation (Intercontinental Marketing Services 2012), the market share of generic medication varies considerably across different countries. This is evidenced by a 2006 study which showed that the market share in Europe varied from less than 10% (Ireland, Greece and Finland) to almost 80% (Latvia and Poland). 80% is considered to be the maximum expected rate of generic prescribing (Dunne et al. 2013). In South Africa utilisation of generic medication is increasing, as reported by

Mediscor (Bester, Badenhorst 2012). Their report on a sector of private healthcare indicates an increase in generic medicine utilisation from 50.0% in 2010 to 53.4% in 2012.

Of interest is why there is such variability in the generic market share. There are multiple influencing factors, many of which fall under the classification of 'pro-generic' policies. These are detailed below.

Pro-generic pharmaceutical policies

Economics of the pharmaceutical market do not adhere to standard economic principles. Intellectual property rights (patent protection), third-party payments, asymmetrical information and low price elasticity distort the market. Consequently policy measures, to ensure efficient dispensing combined with controlled expenditure, have been implemented to different degrees across many countries. Many of these policies encourage generic medicine utilisation, as generic drugs are considered to have a price advantage.

A range of pro-generic policies is used to attempt to control healthcare expenditure. They include demand and supply-side policies that aim to encourage generic entry and generic competition (Hawkins 2011). Typically supply-side policies are easier and hence more readily implemented (Kanavos, Costa-Font & Seeley 2008).

The various pro-generic policy options are detailed in Table 1.

Table 1: Generic pharmaceutical policies

Supply-side policies	
Pricing and reimbursement policies	Reference pricing
	Price caps and controls
	Price controls
Regulatory and IP policies	Fast-track approval
	Bolar provision
	TRIPS patent flexibilities - Compulsory licensing
	First mover advantages - First generic protection with market exclusivity period
Demand-side policies	
Physician-directed policies	
Financial Non-financial	Budgets
	Promoting generic prescribing: Compulsory generic prescribing or Prescribing by generic name.
	Computerized support: on-line price and prescribing/dispensing information
	Prescribing monitoring and audit
Pharmacy-directed policies	
Financial	Pharmacy dispensing mark-ups where incentive is increased profitability for lower cost items (generics) e.g. Regressive margins
	Keep portion of discounts for dispensing cheaper products
	Negotiated income targets
Non-financial	Promotion of generic substitution
	Compulsory generic substitution
	Computerized support: on-line price and prescribing/dispensing information
	Prescribing monitoring and audit
Patient-directed policies	
Financial	Reference-pricing
	Patient cost-sharing - differential or tiered co-payments
Non-financial	Patient education to increase awareness of generics, costs and co-payments

Adapted from Kavanos et al., 2008. Competition in off-patent drug markets: Issues, regulation and evidence, Economic Policy, July 2008

Supply side policies

These include strategies to increase the entry of generics into the market by influencing the reimbursement of medicines, the market price of medicines and/or the regulation of market authorisation.

Internal reference pricing is a system in which the level of coverage is defined - a fixed maximum reimbursement amount is set for clusters of bio-equivalent or therapeutically comparable drugs, but no restrictions are enforced on the manufacturers' price (Aaserud et al. 2006, Organisation for Economic Co-operation and Development (OECD) 2008). Internal reference pricing is described in detail later in this review.

Market prices may be influenced through price caps as applied in France where the price of generics must be 30% less than originator; the UK applies a maximum price scheme for select generic medicines to address supply chain issues. This however has its problems as the maximum price is set too high in some cases as it does not accommodate or promote competition on price (Kanavos, Costa-Font & Seeley 2008).

Although regulatory restriction of market authorization is often seen to hinder generic entry, certain provisions may increase generic entry. These include fast-tracking of regulatory approval of generic medication. Other pro-generic regulatory policies include the Bolar provision which allows generic companies to complete regulatory requirements including bioequivalence studies before an originator's patent has expired (Kanavos, Costa-Font & Seeley 2008) and compulsory licensing which allows a third party to produce the patented product or process without the consent of the patent owner. First-mover advantage encourages the launch of generic drugs by allowing a market exclusivity period (Kanavos, Costa-Font & Seeley 2008). An example is the US Hatch-Waxman legislation through which first-to-market generics get a 6-month exclusivity period (Kaplan et al. 2012).

Demand-side policies

These include prescribing and dispensing policies. They may be financial or non-financial incentives and may be doctor-, pharmacist- or patient-driven. Incentives to prescribe and

dispense generics are typically required as prescribers are more likely to use an originator product.

- *Physicians* largely drive the demand for medicines through prescribing and education of patients. Influencing their prescribing habits and education of patients can impact generic utilisation and cost.
 - Financial physician incentives may include budgets with penalties or rewards to incentivise doctors to control costs. These have been successful in increasing generic market shares in Spain (Costa-Fonta, Puig-Junoy 2004, von der Schulenburg, Vondoros & Kanavos 2011). However this is only successful if budgets are fixed with clear, enforceable guidelines and rules. Modest increase in generic prescribing and achievement of targeted savings has been seen in the UK's former general practitioner fundholding budgets (Kanavos, Costa-Font & Seeley 2008). The concern with budgets is both financial and ethical, as there is a risk of quality issues if the financial incentive is too great.
 - Non-financial physician incentives aim to promote or force generic prescribing/treatment. Prescribing by International Non-proprietary Name (INN) or generic name is seen to successfully increase generic utilisation. In the UK 83% of all prescriptions in 2009 and 2010 were generics, the key driver being the impact of government policy which promotes prescribing by INN in medical training and ongoing practice (Dunne et al. 2013). INN prescribing was similarly phased in from 2001 in Spain. This has been well accepted, impacting 35% of Andalusian pharmaceutical spending with a net effect of reducing the average cost per script to 1% below the Spanish average (Costa-Fonta, Puig-Junoy 2004). Computerized support which provides on-line price and prescribing/dispensing information and prescribing monitoring (von der Schulenburg, Vondoros & Kanavos 2011) and audit (Kanavos, Costa-Font & Seeley 2008) may also improve generic prescribing.
- *Pharmacists* have a role in dispensing generic medication and educating consumers.
 - Financial pharmacy incentives include dispensing mark-ups which promote increased profitability for lower cost items (generics). These may be progressive margins such as flat fee per prescription (Kanavos, Costa-Font & Seeley 2008) or regressive margins where a higher percentage is paid on lower cost items. Most EU countries have

implemented this policy. In Belgium, regulations ensure that profits on generics equal profits on originator drugs in absolute terms (Simoens et al. 2005). Other pro-generic financial incentives include negotiated income targets for pharmacists (Kanavos, Costa-Font & Seeley 2008) and claw-backs. Claw-back policies are applied when manufacturers or wholesalers provide covert discounts to pharmacies. A healthcare insurer claws back a portion of this discount (Kanavos, Costa-Font & Seeley 2008).

- Non-financial incentives including generic substitution policies, which may encourage/promote or oblige/enforce pharmacies to substitute originator products with generics, are successful in increasing generic utilisation (von der Schulenburg, Vondoros & Kanavos 2011). Generic substitution policies are implemented in many countries, including LMIC such as South Africa, Argentina, Bolivia, Chile, Columbia, Ecuador, Jamaica, Mexico, Peru and Uruguay. However there are no LMIC studies to support the effectiveness of this policy in these countries (Faden et al. 2011). As with doctors, computerized support and prescribing monitoring and audit have also been shown to improve generic prescribing.
- *Patient-directed* policies may also impact generic utilisation
 - Financial policies include internal reference-pricing, where the consumer pays a surcharge or co-payment if the dispensed medication is more expensive than the reference price. This co-payment can however be avoided if a product at or below the reference price is dispensed. Patient cost-sharing shifts some of the financial responsibility onto the patient in an effort to encourage use of cheaper generics. This cost-sharing may be in the form of tiered or differential co-payments (a generic drug may have a lower percentage co-payment compared to a branded drug). Non-tiered co-payments such as co-insurance (some consumers may be exempt e.g. France and Spain), a fixed or flat-rate fee per prescription (Mossialos, Mrazek & Walley 2004, Austvoll-Dahlgren et al. 2008) do not however encourage generic use as a fixed amount is paid irrespective of the drug type (Kanavos, Costa-Font & Seeley 2008).
 - Non-financial policies include patient education to increase awareness of generics, costs and co-payments.

In practice pro-generic policies vary in their effectiveness due to the complex combinations that are implemented with different degrees of vigour as well as efforts to address barriers to implementation of these policies (Kanavos, Costa-Font & Seeley 2008). Common to all pro-generic policy implementation is poor monitoring to evaluate their effectiveness and consequently the appropriate mix that collectively promotes generic competition, encourages generic market entry and penetration and reduces overall healthcare expenditure is not clearly understood.

Determinants and Impact of Generic Market Entry and Penetration

Entry of a generic to a market depends on expected profits (Moreno-Torres, Puig-Junoy & Borrell 2009), which are determined by the extent of price regulation and price competition, and related barriers to entry. Price regulation may have the unintended consequence of prices being set higher due to concerns that low prices will be difficult to increase at a later stage. In the US for example where medicine prices are not regulated and price competition is significant, generic prices are seen to decrease substantially over time and have been seen to gain market sales of 50% within the first year of launching (Kanavos, Costa-Font & Seeley 2008). Kavanos et al report that the average generic launch price in the US was 25% less than the originator, and decreased to 20% of the initial average generic price (Kanavos, Costa-Font & Seeley 2008). However the impact of generic entry on the originator price is not as clear, and in certain cases appears to be independent of generic competition. This is often attributed to demand-side brand loyalty. Some studies have demonstrated the 'generic paradox' effect in which originator prices increase with the launch of a generic (von der Schulenburg, Vondoros & Kanavos 2011); whereas other studies report that originator prices don't decrease but their inflationary increase slows down (Kanavos, Costa-Font & Seeley 2008, von der Schulenburg, Vondoros & Kanavos 2011). However, where other policies such as reference pricing co-exist, generic entry does appear to have a competitive effect on the originator price (Kanavos, Costa-Font & Seeley 2008).

Other barriers to entry and penetration of generics include first mover advantages, non-transparent discounting and other demand-side incentives as well as originator drug marketing strategies (Kanavos, Costa-Font & Seeley 2008). These are detailed under the 'marketing strategy' section below.

Generic market entry has been positively associated with the potential market size, which relates to anticipated profits and the number of generic companies, the age of the market and the number of branded products (copy or licensed) (Moreno-Torres, Puig-Junoy & Borrell 2009). The impact of reference pricing on generic entry is detailed later in this literature review.

Several studies have indicated that issues which impact generic *penetration* are patent protection policies and the extent of price regulation (Magazzini, Pammolli & Riccaboni 2004). Policies that encourage price competition have been seen to be effective in increasing generic penetration (e.g. USA), whereas environments in which prices are highly regulated appear to limit generic diffusion (e.g. Spain: 2006 IMS data indicates a market share for generics 14.6% in volume, and 7.9% in value) (Magazzini, Pammolli & Riccaboni 2004, Moreno-Torres, Puig-Junoy & Borrell 2009).

Kavanos et al. (2008) summarize the effects of generic entry in Table 2.

Table 2: Impact of expiry of originator brand patent and generic entry

Variable	Effect	Comment
Price of originator brand	Likely to increase	Effect holds if there is no regulation
Price of generic drug	Declines	Extent of decline is unclear and may depend on regulation
Volume or market share of originator brand	Declines	Decline is significant and may at times reach zero
Volume or market share of generic drug	Increases	Takes up most of the originator market share, but may not increase significantly due to potential switch effects
Number of generic entrants post patent expiry and their effect	Increases	Effect on generic price and generic penetration is ambiguous
Savings to health insurance from greater generic use	Should increase significantly	No evidence exists at systemic level; available evidence pertains only to ad hoc estimation of individual policy measures

Source: Kavanos et al. 2008. Competition in off-patent drug markets: Issues, regulation and evidence. *Economic Policy*. vol. 23, no. 55

Marketing Strategies

Originator pharmaceutical companies are continuously trying to minimize the increasing market share of generic drugs. A 2009 European Commission of Inquiry into the pharmaceutical sector indicated that while factors such as regulatory framework play an important role in obstacles to generic market entry, it established that the behaviour of originator companies has a profound impact on market entry. It describes the 'tool-box' of armaments that originator companies use in response to generic entry. The European Commission lists the following 'instruments and measures' that are used by originators (European Commission 2009, p. 16):

- “patenting activities,
- contacts, disputes and litigations between originator and generic companies,
- opposition procedures and appeals before patent offices,
- patent settlements and other agreements between originator and generic companies,

- interventions of originator companies before national authorities deciding on marketing authorisation, pricing and reimbursement of generic products,
- promotional activities, and
- second generation products.”

In addition originators may also develop, launch and market patent-protected therapeutic alternatives (Simoens et al. 2005, Galizzi, Ghislandi & Miraldo 2011).

The European Commission, in its Pharmaceutical Sector Inquiry Final Report, defines second generation products, also referred to as ‘follow-up’ products, as “products that result from follow-up R&D essentially based on that of an existing product ("first product") and have essentially a similar mode of action. These second products may have the same INN (International Non-proprietary Name) as the first product (e.g. second products involving inter alia new formulations, crystalline forms, particle sizes or medical uses) or a different one (e.g. combinations, individual stereoisomers separated from mixtures or the identification of metabolites of an existing INN).” (European Commission 2009, p.351) Industry frequently refers to these as ‘me-too’ or incremental innovation drugs.

In addition to the launch of ‘me-too’ and other on-patent innovative products, an increasing trend seen in many countries, including South Africa is the launch of ‘authorised generics’ (AGs), also referred to as ‘clones’ or ‘auto-generics’. AGs, as defined in a report by the Federal Trade Commission are “pharmaceutical products that are approved as brand-name drugs but marketed as generic drugs.” (Federal Trade Commission 2011, p. 3). They have alternative names to their generic brand-name counterparts and are manufactured either by the originator company or by another pharmaceutical manufacturer through acquisition or joint venture. They are frequently launched prior to the originator’s patent expiry. This is based on the concept of the ‘first-mover advantage’ in which the first generic launched is able to gain substantial market share at a higher price than that of later generics. As the quality of the AG is perceived to be higher than that of later entrants, first entrant prices can be maintained at a higher level and products may retain market share for a longer period of time (López-Casasnovas, Puig-Junoy 2000).

The implementation of 'pay-for-delay settlement' is another strategy to minimise the impact on originator drugs. In this agreement a brand-name company pays a generic manufacturer to delay their launch of a generic together with the promise not to launch an AG. This is particularly prevalent in the US where the first generic filed gets a 180-day exclusivity period when no other generic may launch. AGs are not subject to this exclusivity (Federal Trade Commission 2011).

The response to the launch of a first-time generic often favours originator products and the perception of generics is frequently negative. This is as a result of a combination of factors including:

- imperfect information regarding the quality of generics due to a poor understanding of the regulatory requirements for the registration of generic medicines;
- brand loyalty to originators and risk aversion based on provider and patient experience gained during the on-patent period (López-Casasnovas, Puig-Junoy 2000);
- the launch of originator 'me-too' products in competition with generics combined with strong sales and marketing force of originator products (Galizzi, Ghislandi & Miraldo 2011).
- the lack of incentive to move to generics (López-Casasnovas, Puig-Junoy 2000).

South African pharmaceutical policies that impact generics

In South Africa medicines are highly regulated, affecting market structure and competition. Policies that impact the entry and penetration of generics into the market are detailed below.

- Drug registration: All scheduled medicine must be registered by South Africa's Medicine Controls Council (MCC) prior to marketing the product in South Africa. The MCC determines the scheduling status of medicines and approves products on the basis of efficacy and quality of the production facility. Pharmacoeconomic evaluation information for new chemical entity medicines and for new indications for existing medicines is currently required on a voluntary basis. Any 'interchangeable multi-source medicine' (generic) must prove bioequivalence to the originator to get registration approval.

Registration processes are notoriously slow, although there is an accelerated review process to fast track the registration process for specific medicines that have important therapeutic benefit and which are required urgently to deal with key health problems. The turnaround times for registration of generic medication is reported to be faster than that of innovative products (Crasto 2014).

- Draft changes to Intellectual Property regulations were published in September 2013. A change in the Patent Act to incorporate ‘patent flexibilities’ as contained in the TRIPS Agreement is proposed to ensure that the Act is amenable to issues related to access to public health. ‘Patent flexibilities’ include compulsory licensing, which allows a third party to produce the patented product or process without the consent of the patent owner (Department of Trade and Industry 2013).
- Price regulation: In the past decade several regulatory interventions and policies have been implemented in an effort to control medicine prices. The Department of Health (DoH) has indicated that the aim of the regulatory interventions is to “Protect the South African health system from paying distorted prices for medicines through the elimination of price distortions and price distorting behaviour” (Department of Health 2010a). Pricing regulation and related policies are as follows:
 - Single Exit Price (SEP) was introduced in 2004. This requires that manufacturers or importers of medicines sell scheduled medicine at the same price to all purchasers with the exception of the State. Manufacturers were required to submit their initial SEPs based on a calculation adjusted for discounts previously given and taking into account the price of the product in other countries where medicine prices were regulated. The SEP includes the logistics fee which may be negotiated between the manufacturer and logistics providers/distributors. SEP increases are only allowed on an annual basis. The quantum of the increase is guided by a published formula, but the final increase is determined annually by the Pricing Committee (Department of Health 2004a). Legislated SEP increases are detailed in Table 3; these are the maximum that a SEP may be increased. Of note is that a zero percent increase was applied in 2005, 2006 and 2011. SEP decreases, either temporary or permanent can be made at any time through application to the DoH.

- Rebates, discounts and other incentive schemes offered by manufacturers to providers have been prohibited since 2004 (Department of Health 2004b).

Table 3: Legislated Single Exit Price increases

Year	Quantum of Increase
2005	No increase
2006	No increase
2007	5.2%
2008	6.5%
2009	13.2%
2010	7.4%
2011	No increase
2012	2.14%
2013	5.8%

Source: (Department of Health 2006, 2008a, 2008b, 2010b, 2011, 2013)

- Dispensing fees were regulated in 2004, but were contested in court and only finally implemented in December 2010 for pharmacists. These are reviewed annually. The dispensing fees are based on a tiered structure and are considerably higher for more expensive drugs. Consequently this could result in a disincentive for a pharmacy to dispense cheaper products e.g. cheaper generics. Dispensing fee regulations and licensing restrictions are also in place for non-pharmacists such as doctors and nurses.
- Draft regulations for the introduction and methodology of international benchmarking (external reference pricing) of originator medicine prices have been published (May 2014) but not yet implemented. Australia, Canada, New Zealand, Spain and South Africa as proposed as benchmark countries (Department of Health 2014). Regulation of logistic fees that manufacturers pay for the distribution of medicines has also been published but not finalised.
- There are no specific pro-generic pricing or reimbursement policies. No national system of GRP is in place in South Africa. However in the private insurance industry

both GRP and therapeutic reference pricing (TRP) are applied, sometimes simultaneously. Whereas only some administrators and schemes TRP, mostly for chronic medication, GRP is frequently applied. In 1987 MediKredit Integrated Healthcare Solutions (“MediKredit”), a pharmacy benefit manager, implemented the first GRP model called “Maximum Medical Aid Price” (MMAP) (Author’s industry knowledge). This model soon became the industry norm. Subsequently multiple GRP models have been implemented by different medical scheme administrators and pharmacy benefit managers. Table 4 lists the names and custodians of some of the different models.

Table 4: Generic reference pricing models in South Africa’s private healthcare insurance market

Reference Pricing Model Name	Abbreviation	Custodian
Careware Average Price	CAP	Liberty
Maximum Medical Aid Price	MMAP	MediKredit Integrated Healthcare Solutions
Medicine Price List	MPL	Medscheme Holdings
Mediscor Reference Price	MRP	Mediscor
Qualsa Maximum Price	QMP	Qualsa Healthcare (Metropolitan Health Group)

Source: Based on author’s industry knowledge

Each GRP model is based on a different methodology with varying frequencies of updates. Consequently the industry is subjected to multiple different GRP categories each with varying reference prices. Although most pharmacies and dispensing doctors use third party practice management software which typically updates the reference prices for the various GRP models, it is surmised that the full value of the GRP is undermined by the complexity of multiple models. As medicine is frequently reimbursed by a third party, prescribers are often less aware of the cost of prescribed medicine and available generic alternatives as well as the varying reimbursement limits of the different GRP models.

- The only pro-generic demand side policy that is in place in South Africa at a national level is mandatory generic substitution which was implemented in 2003 (Deroukakis 2007). This legislation requires that pharmacists or other dispensers of medication are obliged to inform patients of the availability of ‘interchangeable multi-source medicine’ (generic) alternatives as a substitute for the branded medication prescribed by their doctor and

dispense a generic alternative, unless the doctor has specifically indicated that substitution should not take place, the patient declines a generic or the price of the generic is higher than that of the branded product. At the time the Medicines Control Council (MCC) maintained a list of products that were considered non-substitutable. This list has subsequently been withdrawn.

- Other pro-generic policies in place are typically driven by private funders of health care in an effort to reduce medicine costs. These include the use of treatment protocols and/or formularies as well as the appointment of ‘designated service providers’ (DSPs) for the provision of specific services and regulations relating to the implementation of prescribed minimum benefits (PMBs). The PMBs are a set of benefits for which a medical scheme is obliged to pay in full, including the diagnosis, treatment and care costs. Generic prescribing and dispensing may be a pre-requisite for participation as a DSP for the supply of medicine. Manufacturers compete for inclusion on formularies and negotiations are complex as a manufacturer needs to take into account a wide variety of the formularies and reference pricing models, each with different member impact and implementation dates as well as the manufacturer’s DSP arrangements.
- The South African private healthcare market is subject to multiple pharmaceutical pricing regulations as well as medical insurer PMB and DSP requirements. The complexity of these policies is enhanced by the fragmentation resulting from a multitude of different insurers that apply additional customized pharmaceutical policies.

Reference pricing

Definition

Reference pricing may be external or internal. External reference pricing is a price control mechanism, whereas internal reference pricing is a method of reimbursement by setting a ceiling for health insurers. These are defined in more detail below.

External reference pricing or international benchmarking is defined as “the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given

country". It is the most commonly used pricing policy in Europe, being used by 87% of European countries (Leopold et al. 2012).

Internal reference pricing is a system of controlled reimbursement in which a maximum reimbursement price is set by a third party insurer for a defined group or cluster of medicines. The difference between this reference price and the price of the prescribed drug, if higher, is paid by the patient. This out-of-pocket (OOP) payment is often referred to as cost-sharing (Aaserud et al. 2006). Patients are made aware of drug prices and are made to bear some responsibility for higher cost drugs, thus transferring risk from the funder to the patient. Unlike fixed co-payments, patients can choose to avoid a co-payment as they have the option to switch to a lower-cost drug at or below the reference price (Aaserud et al. 2006, Miraldo 2009, Moran 2010, Galizzi, Ghislandi & Miraldo 2011). However, the desired outcome is that the patient switches to a cheaper alternative, thus reducing the overall cost of the drug.

Different terms used for reference pricing include maximum allowable costs, best available prices and minimum pricing (Aaserud et al. 2006). Reference pricing is sometimes referred to as "index pricing", however with index pricing the pharmacist is incentivized to dispense the lowest cost drug in the index cluster as the pharmacist pockets the difference between the index price and the dispensed drug price (Aaserud et al. 2006, Brekke, Grasdal & Holmas 2009).

Although it is not strictly a pricing policy, reference pricing can have an impact on manufacturers' pricing policies as the manufacturer has an incentive to price below the reference price (Dylst, Vulto & Simoens 2011). As such it may be referred to as an indirect method of price control (Aaserud et al. 2006).

Internal reference Pricing Objectives

The objective of reference pricing is to promote rational use of interchangeable drugs to control overall pharmaceutical expenditure with no associated negative health outcomes (López-Casasnovas, Puig-Junoy 2000, Golob, Molj & Podnar 2007) and no discriminatory effects (Miraldo 2009). The success of this objective depends on the effectiveness of reducing the demand for higher-priced products (demand-side approach) while simultaneously encouraging product price cuts, thereby stimulating price competition (supply-side approach)

(Puig-Junoy 2005, Brekke, Grasdal & Holmas 2009). Management of demand is achieved by creating price-sensitivity and restraint in prescribers, dispensers and consumers of medicine by exerting financial pressures on consumers through cost-sharing of dispensed products priced above the reference price. Price competition is created by inducing pharmaceutical firms to reduce prices around the reference price to ensure that market share is not lost (López-Casasnovas, Puig-Junoy 2000, Aaserud et al. 2006). However, because of information asymmetry, moral hazard, provider incentives and heterogeneity that typify healthcare markets, demand for healthcare is frequently determined by providers. Consequently control of supply is often more effective than control of demand (Mossialos, Mrazek & Walley 2004).

Types of internal reference pricing

Three basic types of reference price clusters or drug groupings are typically described. The equivalence criteria of the cluster determine the type of reference pricing. These clusters are determined by chemical, pharmacological or therapeutic equivalence and are often referred to as different levels or phases of reference pricing (see Table 5).

Table 5: Comparison of different levels/phases of internal reference pricing

Level/ phase	Type of Reference Pricing (RP)	Cluster equivalence criteria	ATC level	Comparability of cluster drugs
1	Generic RP (GRP)	Identical bioactive ingredients, as demonstrated by bioequivalence studies	ATC level 5 e.g. C10AA05: Atorvastatin	Therapeutically interchangeable
2	Therapeutic RP (TRP)	Pharmacological class	ATC level 4 e.g. C10AA: HMG CoA reductase inhibitors	Chemically slightly different; similar pharmacological benefit; comparable or identical indication
3	Therapeutic RP (TRP)	Therapeutic class	ATC level 3 e.g. C10A: Lipid modifying agents, plain	Comparable therapeutic effect but not necessarily chemically or pharmacologically similar

Source: Collated from Galizzi 2011; Aaserud et al. 2009

In generic reference pricing (GRP) (Level 1 reference pricing), also referred to as molecular reference pricing, chemical equivalence criteria are applied. Included products typically have

the same active ingredient, strength and route of administration as an off-patent originator drug and are generally considered interchangeable (Aaserud et al. 2006, Galizzi, Ghislandi & Miraldo 2011). These clusters are within the same Anatomical Therapeutic Chemical (ATC) level 5 group. Different salts and esters as well as comparable dosage forms e.g. tablet and capsule may be considered interchangeable. Products with different bioavailability across brands such as drugs with narrow therapeutic indices for which a change in preparation may result in toxic or sub-therapeutic doses may be regarded as exclusions to the criteria (Moran 2010). Critical to the implementation of GRP is concise inclusion and exclusion interchangeability criteria.

Level 2 therapeutic reference pricing (TRP) may include clusters of drugs that are chemically different but pharmacologically similar with similar molecular structure, similar pharmacological benefits and similar or identical indications. This typically includes products that are classified within the same level 4 ATC structure.

Level 3 TRP is the broadest definition where clusters can be therapeutically similar and include all drugs to treat a specific condition (Aaserud et al. 2006, Galizzi, Ghislandi & Miraldo 2011). Included drugs, usually in the same ATC level 3 classification, are not necessarily similar biochemically or pharmacologically, but they have comparable therapeutic effects (Dylst, Vulto & Simoens 2011).

Although each type of reference price has its own advantages, there are disadvantages at each level. GRP (level 1) may result in a prescription for a patented drug that is not subject to reference pricing in order to avoid a co-payment. Ultimately this will drive costs up further. Therapeutic reference pricing, on the other hand, may prompt the prescribing of a less appropriate drug with negative clinical consequences in order to avoid a co-payment (Dylst, Vulto & Simoens 2011).

Practically reference pricing has been implemented in many shapes and forms. Policies and criteria that determine the impact of the RP include:

- Level of reference pricing and equivalence criteria
- Implementation of a combinations of reference pricing levels
- Eligible therapeutic groups

- Methodology to determine the quantum of the reference price and frequency of review
- Inclusion/exclusion of patented drugs
- Incentives for prescribers and dispensers
- Exceptions and exclusion policies
- Type and level of co-payment
- Pricing regulation policies, including internal regulation and external reference pricing (benchmarking)
- Generic substitution policies e.g. forced substitution
- Parallel importation policies (Puig-Junoy 2005).

The flexibility of implementation of reference pricing is a benefit as it can be customized to specific requirements. However this heterogeneity has its disadvantages in that it becomes increasingly challenging to determine the impact of the various policies, either alone or in combination.

Country analysis

In this section I provide a high level overview of reference pricing systems that are currently in place across the globe to illustrate the variability that exists. The objective is not to provide a comprehensive analysis as this in itself would be a dissertation.

Generic and therapeutic reference pricing is widely adopted across the globe however its implementation varies considerably. Table 6 illustrates this variability, highlighting the different levels of reference pricing, pricing methodology and regulations of various countries.

Reference pricing, particularly GRP, is a common pharmaceutical policy in many countries. It was first implemented in the state of Maryland by US Medicaid. The first country to implement RP at a national level was Germany in 1989 (Organisation for Economic Co-operation and Development (OECD) 2008).

In a sample of 26 European countries, 73% apply some form of officially set reference pricing. The majority use chemical equivalence as the RP model, and several countries have varying combinations of TRP and GRP. 54% of this sample of countries also applies price regulation policies on generic medicines (Puig-Junoy 2010).

GRP was implemented in Sweden (1993) and Norway (2003) but has subsequently been withdrawn in both countries. Sweden now applies compulsory substitution with the lowest priced generic GRP (Puig-Junoy 2010). British Columbia, Canada first introduced GRP in 1994 but subsequently moved to TRP.

Table 6 illustrates reference pricing models of various high income countries. As previously indicated there is very little information available on LMICs, and where this is available it is referred to under later sections.

Table 6: Country Analysis of Reference Pricing Models

Country	Year of implementation	RP system	Level of RP	Maximum reimbursement rate	Price regulation of generics	Generic substitution
Belgium	2001	Yes	Chemical (ATC 5)	Initially 17% lower than original; gradually reduced to 30% below price of original product	Generic priced 30% lower than original product	No
Canada	1995	Yes	British Columbia: Initially introduced as GRP in 1994 (Now referred to as 'Low Cost Alternative (LCA) Program' - Chemical 5+4); TRP for specific groups commenced 1995 (called 'Reference Drug Program') (British Columbia Ministry of Health 2012)	LCA program: 20% (solids) or 35% (other formulations) of LCA comparator price.	Yes	Yes
Czech Republic	1995	Yes	Clinical, pharmacological, therapeutic (ATC 5+4)	Lowest price in group	Price < 55% of price of original product	No
Denmark	1993	Yes	Chemical (ATC 5+4)	Lowest price in reimbursement or substitution group	Generic priced lower than original product	Yes
Estonia	2003	Yes	Chemical (ATC 5)	2nd lowest price in group	NA	Yes
Finland	2009	yes	Chemical (ATC 5)	Lowest price plus €1.50	NA	Yes
France	2003	Yes	Chemical (ATC 5)	Average of generics with one active ingredient (Puig-Junoy 2010)	Generic priced 55% lower than original product	Yes
Germany	1989	Yes	Clinical, pharmacological, therapeutic (ATC 5+4); TRP was suspended from 1997 to 2003	Weighted average of existing prices; since 2004 must be above the lowest third of cluster's market prices	No regulation	Yes
Hungary	1999	Yes	GRP introduced in 1999; TRP commenced in 2003 for certain groups; Chemical (ATC 5+4)	Price of cheapest product in group with a cumulative market share of 50%	Generic priced 30% lower than original product and no higher than the reference price	Yes
Italy	2001	Yes	Chemical (ATC 5)	Lowest price in group	Generic priced at least 20% lower than original	Yes

Country	Year of implementation	RP system	Level of RP	Maximum reimbursement rate	Price regulation of generics	Generic substitution
Latvia	2005	Yes	Therapeutic (ATC 5+4+3)	Lowest price in group	NA	Yes
Lithuania	2003	Yes	Chemical (ATC 5)	Lowest price in group	Generic priced 30% lower than original product	Yes
Netherlands	1991	Yes	Level III - Chemical, pharmacological, therapeutic (ATC 5+4+3)	Fixed; Lowest price in group	Price cap benchmarked on average of 4 EU countries	Yes
Poland	1998	Yes	Chemical and pharmacological (ATC 5+4+3)	Lowest price in group	NA	Yes
Portugal	2003	Yes	Chemical (ATC 5)	Price of most expensive generic	Generic priced 35% lower than original product	Yes
Romania	1997	Yes	Chemical (ATC 5)	Lowest price in group	NA	Yes
South Africa	1987	Yes, but only for individual insurers	GRP from 1987; Some insurers have implemented TRP since 2004	Varies across insurers	Single exit pricing regulation applies to generic and original medicines	Yes
Slovakia	1995	Yes	Chemical and pharmacological (ATC 5+4)	Lowest price (per Defined Daily Dose)	NA	Yes
Slovenia	2003	Yes	Chemical (ATC 5)	Price of cheapest generic in group	Yes	Yes
Spain	2000	Yes	Chemical (ATC 5)	Mean of lowest 3 products	Generic priced lower than reference price	Yes
Sweden	1993; discontinued in 2002	Discontinued	NA	Previously, compulsory substitution with lowest-priced equivalent product	Free pricing, with negotiated purchase agreements	Yes

Adapted from Galizzi et al. 2011, Ioannides-Demos et al. 2002 and Moran 2010 unless specified otherwise

The impact of GRP

The effectiveness of reference pricing depends on the policy's ability to modify both supply and demand. How effectively does it promote dynamic price competition and does it encourage financial responsibility of consumers, prescribers, dispensers and pharmaceutical companies (Galizzi, Ghislandi & Miraldo 2011)? The success of reference pricing on these interventions is influenced by multiple factors, some of which are described below:

- The socio-political, funding and legal context, including existing pharmaceutical and healthcare policies such as legislation that enables clearly defined medication interchangeability. These all impact the reimbursement status of medication both before and after implementation of RP.
- The policy design of the reference pricing model plays a major role in its effectiveness. Influencing factors include the equivalence criteria that determine the make-up of a cluster; the inclusion or exclusion of branded products (in the case of TRP) and/or products that may be deemed non-substitutable; the price of the base product(s); the number of products in a cluster; the methodology used in the price calculation and the frequency of RP price reviews (Galizzi, Ghislandi & Miraldo 2011).
- The extent to which stakeholders are involved from an early stage as well as the roll-out of a comprehensive patient communication strategy to ensure acceptance and understanding (Moran 2010).
- Patients' price-sensitivity linked to the quantum of co-payment and patients' willingness to pay OOP together with their perception of the substitutability of generics.
- Prescribing and dispensing provider characteristics: perception of the substitutability of branded product with generics as well as incentives and/or disincentives to substitute. Puig-Junoy reports that in several countries pharmaceutical companies offer large discounts to pharmacies (from 10-70%) but that these discounts are seldom passed on to the consumer. The percentage discount often correlates to the number of generic competitors in the market (Puig-Junoy 2010, 2012). In South Africa discounting and rebates are prohibited however prescribing and dispensing may be influenced by specific manufacturers either through managed care formularies or manufacturer-linked marketing incentives.

- Pharmaceutical market characteristics that may impact RP effectiveness include the quality of generics, the number of generic firms, the number of generic products per category (Galizzi, Ghislandi & Miraldo 2011) and negotiations and arrangements with funders and providers.

In reality measuring the impact of GRP is a complex challenge because of heterogeneous nature of its implementation. There is also a paucity of long-term data (Golob, Molj & Podnar 2007) across all markets with the end result that the jury is still out on the long-term effectiveness and clinical outcomes of GRP. The distinct lack of comparable data is particularly a concern in LMICs. GRP data identified from LMICs are described below.

A study conducted in South Africa assessed the effect when Medscheme administrators introduced their own reference pricing system in 2002. Nearly one year later product prices were seen to increase but the increases were lower when compared to inflation at the time (Rothberg et al. 2004).

In Taiwan GRP with small OOP payments was implemented in their NHI system. Chen et al studied the impact of reference pricing on three cardiovascular drugs. The impact was a 5.8-14.8% decrease in the daily cost of these medicine classes. However drug volumes and the overall expenditure on these drug groups increased significantly (Chen, Chen & Yang 2008).

In Kyrgyzstan the impact of generic reference pricing was a decrease in product prices, resulting in more stable prices of medicines (Faden et al. 2011).

The following section provides an overview of the potential impact of reference pricing, with a specific focus on GRP.

Effect on Product Price

Although reference pricing models are reimbursement systems rather than pricing systems, they are expected to have an impact on drug price. Theoretical studies predict that with the implementation of RP:

- drugs that are priced higher than the reference price will decrease in price as pharmaceutical companies are incentivized to price their drugs at or below the reference price in an effort

to retain or increase market share. The quantum of this decrease depends on the design of the RP model, the number of drugs in a cluster, consumer price sensitivity and consumer perception of the substitutability of generics for brand-name drugs (Brekke, Holmas & Straume 2011, Galizzi, Ghislandi & Miraldo 2011).

- drugs priced below the reference price may increase in price as the RP may be viewed as a target (Dylst, Vulto & Simoens 2011). This is consistent with Danzon and Ketcham (2004)'s theory of 'price convergence' towards the reference price.
- An increase in price may be anticipated in those drugs that have non-referenced therapeutic alternatives, referred to as 'unintended cross-price effects' by Brekke (Brekke, Grasdal & Holmas 2007, 2009, Brekke, Holmas & Straume 2011, Dylst, Vulto & Simoens 2011).

Analyses of 22 empirical studies in OECD countries (GRP and TRP studies) by Galizzi et al. (2011), 23 studies of European countries by Dylst et al. (2011) and 12 studies by Puig-Junoy (2010) largely support these theoretical predictions. The studies illustrate a generalized decrease in product prices in the majority of countries with GRP policies, irrespective of the country's regulatory environment. The impact of GRP on reducing price is however generally much smaller than that of TRP models (Galizzi, Ghislandi & Miraldo 2011). The price decrease often occurs rapidly after GRP implementation, evidenced by data from Germany, Italy, Sweden and Norway (Puig-Junoy, Moreno-Torres 2010, Dylst, Vulto & Simoens 2011). Kavanos et al. report a decline of up to 47% in the lowest generic price, but indicate that if there is no incentive to rapidly decrease prices below RP, average generic prices decrease sluggishly over time (between -1.4% to -2.7%) (Kavanos, Costa-Font & Seeley 2008). In Norway RP was introduced in 1993, but was stopped in 2001 due to insufficient long-term cost saving (Dylst, Vulto & Simoens 2011). More significant price reductions were observed for those drug categories which had generics available before implementation of RP (Galizzi, Ghislandi & Miraldo 2011). In addition, price decreases have been positively correlated with the number of generic categories (Puig-Junoy, Moreno-Torres 2010).

GRP is seen to have similar effects when implemented in LMICs. In South Africa, the implementation of GRP for a privately insured population resulted in retarding the inflation rate of impacted medicines – the price of more than 50% of formulary drugs either decreased or did not increase after 1 year (Rothberg et al. 2004). In Kyrgyzstan reference pricing was also seen to decrease and stabilize medicine prices (Faden et al. 2011).

The decrease in price is however noted to be asymmetrical within a reference category – the analyses described above demonstrated that products priced above the reference price, in particular original branded products, tended to decrease in price whereas frequently products at or below the reference price remained unchanged, indicating an absence of price competition below the RP (Puig-Junoy 2010, Galizzi, Ghislandi & Miraldo 2011). This however is contrary to the theory termed the ‘generic paradox’, expounded by Scherer, which suggests that the price of originator drugs increases with the introduction of RP due to prescriber brand loyalty (López-Casasnovas, Puig-Junoy 2000). Slovenian and Hungarian studies partially support this theory as the price of several original products did not decrease with the launch of generic products and the implementation of reference pricing (Golob, Molj & Podnar 2007, Dylst, Vulto & Simoens 2011). Similarly a study of six European countries suggested that RP had a positive effect on originator drugs (von der Schulenburg, Vondoros & Kanavos 2011). The asymmetry of price impact is also seen in products that have prices below the RP - in the Netherlands it was observed that some drugs raised their price to the level of the reference price (Dylst, Vulto & Simoens 2011), as predicted by theory.

A study from Spain illustrates the saturation point of the impact of RP – once drug prices had fallen to the level of the RP, almost no products reduced their price until such time as the reference price was adjusted downwards (Puig-Junoy 2010, Dylst, Vulto & Simoens 2011). Galizzi et al also report on the positive impact of repeated and persistent reductions of the RP on product price (Galizzi, Ghislandi & Miraldo 2011).

The impact of reference pricing cannot, however, be viewed in isolation as typically RP models are implemented in conjunction with a range of other price reducing strategies. A study by the European Commission (2009) showed that price reductions were greater when GRP is combined with mandatory generic substitution and when reference prices are regularly revised.

It must be noted that while reference pricing and other pro-generic policies do encourage market entry of generics and reduce prices, data from countries such as the United Kingdom and United States which have no price regulations, suggest a more rapid decline in generic prices. Thus competitive forces may have a greater impact on prices compared to price regulation (Kanavos, Costa-Font & Seeley 2008, Simoens 2012).

Effect on Drug Utilisation and Market Share

Theoretical modelling confirms that the introduction of RP increases the use of drugs which are included in the reference cluster, that are priced at or below the RP. This impacts the percentage share of the generic and brand-name markets (Miraldo 2009, Dylst, Vulto & Simoens 2011). However the impact of RP on drug use and market share is dependent on numerous factors, including but not limited to the time of introduction, the price response of the manufacturers of original drugs, frequency of updates, the method of calculation of the RP (Golob, Molj & Podnar 2007, Puig-Junoy 2007) and marketing strategies of originator and generic medicines. For this reason there is a lack of clear-cut evidence on the true impact of GRP.

If brand-name drugs do not adjust their price to RP levels, generic utilisation and consequent market share is seen to increase significantly, resulting in a wider price differential between generics and originators (Ghislandi, Krulichova & Garattini 2005, Aaserud et al. 2006, Golob, Molj & Podnar 2007, Galizzi, Ghislandi & Miraldo 2011). An example of this impact was the introduction of RP for Lisinopril in Belgium, where there were two originator products, Zestril® and Novatec®. Zestril®, which dropped its price to that of the generic, increased its market share by 15%, whereas Novatec®, which didn't adjust its price, decreased in market share by 43% (Simoens et al. 2005). Although generic utilisation in Belgium is comparatively low, the average generic market share was noted to increase from 2.05% of the total market in the 3.5 years preceding GRP implementation to 6.11% in the 3.5 years post-implementation. New generics launched showed an initial increase in market share which stabilised after a few months (Simoens et al. 2005). Generic drug use may however be hampered where 'price convergence' towards the reference price occurs, as generic products lose their price advantage over the originators (Puig-Junoy 2005, 2007). In Spain reference pricing appears to have discouraged generic entry. This was specifically noted when the Spanish reference pricing model was changed in 2004 to oblige pharmacists to substitute the lowest priced generic. This had the effect of forcing brand-name drugs to reduce their prices to the reference price level which discouraged generic price advantage (Moreno-Torres, Puig-Junoy & Borrell 2009).

To counter the impact of RP, originator companies use a host of strategies to impact generic use and minimize generic market share. Several of these strategies were described under the section 'Marketing Strategies' above.

Reference pricing may encourage a switch to patented products - GRP may lead to a reallocation of demand with patients moving from older, less expensive off-patent drugs to newer, more expensive on-patent products which do not attract GRP co-payments (Ghislandi, Krulichova & Garattini Dylst 2005, Vulto & Simoens 2011, Galizzi, Ghislandi & Miraldo 2011). This was observed in the Netherlands where patients moved to on-patent proton pump inhibitors (PPIs) such as esomeprazole instead of using generic omeprazole (Dylst, Vulto & Simoens 2011). However no analysis is available that determines whether this switching is due to GRP or other circumstances.

Effect on Expenditure

Empirical studies, including studies in Belgium, Italy, Norway, Sweden and Spain show a significant reduction (up to 50%) in expenditure on pharmaceuticals subject to GRP, particularly in the short-term (Ghislandi, Krulichova & Garattini 2005, Simoens et al. 2005 Puig-Junoy 2007, Galizzi, Ghislandi & Miraldo 2011). As an example, in Belgium the introduction of GRP in 2001 lead to a savings of 7.3% from 2001 to 2002 in pharmaceutical expenditure where a generic was available. The source of savings includes a decrease in the price paid by the funder due to the reference price cap; a decrease in the price paid by the consumer for reference medicines; a decrease in co-payment and increase in use of generics where patients opt to use products that are at or below the reference price; and lower costs of pharmacy stock (Moran 2010).

However GRP may not lead to long-term savings in pharmaceuticals subject to GRP or in savings in total pharmaceutical expenditure (Chen, Chen & Yang 2008, Dylst, Vulto & Simoens 2011, Galizzi, Ghislandi & Miraldo 2011) for various reasons, including:

- GRP by definition can only apply to the limited number of medicine categories for which generic products are available;
- Changes in prescribing habits - over time there is a reallocation of demand to on-patent products which do not attract GRP co-payments; an increase in volume of drugs dispensed within a cluster, as reported by Chen et al. (2008).
- RP only impacts price and not utilisation (Dylst, Vulto & Simoens 2011).

Impact on Out of Pocket (OOP) Payments

Moral hazard refers to the insurance risk that arises when an insured party's behaviour changes as a result of being insulated from risk. Typically utilisation and/or costs increase. In the case of pharmaceuticals, cost-sharing policies such as reference pricing OOP payments, flat-rate co-payments, coinsurance, deductibles and differential co-payments may be implemented to reduce this moral hazard as demand is frequently responsive to price and related cost-sharing (Austvoll-Dahlgren et al. 2008).

Several studies have shown a decrease in demand with the implementation of cost-sharing policies. An Italian study based on a natural experiment showed a 4% reduction in per capita volumes prescribed and a 3.4% reduction in public expenditure with a 1 Euro increase in a fixed co-payment. Similarly a 1 Euro reduction in co-payment resulted in an increase in per capita prescribed volumes and expenditure of 3.4% and 4.9% respectively (Fiorio, Siciliani 2010).

The concern raised with GRP is that patient demand is frequently determined by providers. Because information asymmetry typifies healthcare, patients may inadvertently claim a more expensive alternative based on a doctor's prescription or as determined by a pharmacist's available stock. In addition equity in healthcare may be reduced as cost-shifting is directed to individuals who may not be able to cost-share (Mossialos, Mrazek & Walley 2004).

Equity concerns are frequently raised as cost-sharing may not be voluntary on the part of the patient and low income patients may be forced to default on treatment due to the inability to pay OOP (Mossialos, Mrazek & Walley 2004).

Impact on Health Outcomes

Theoretical modelling by Brekke *et al.* (2011) suggests the possibility that both GRP and TRP may negatively impact health outcomes by inducing trade-offs between the co-payment and the potential health advantages. Brekke also postulates that RP may decrease research and development into innovative drugs which could ultimately have a positive impact on health outcomes. On the other hand their model also suggests that RP may reduce the price of 'me-too' drugs, which could then force pharmaceutical companies to invest in innovative drugs (Brekke, Holmas & Straume 2011, Galizzi, Ghislandi & Miraldo 2011) which ultimately may have a positive impact on health outcomes.

Most literature reviews and studies argue that because of the bio-equivalence requirements of GRP, it should not have a systematic effect on health outcomes (López-Casasnovas, Puig-Junoy 2000). Dylst comments that there may be an impact on adherence if co-payments are onerous; however this is less of an issue with GRP where products are interchangeable (Dylst, Vulto & Simoens 2011). A survey in British Columbia indicated that 75% of physicians reported a deterioration of patient symptoms when moved to a bio-equivalent product (López-Casasnovas, Puig-Junoy 2000). Unfortunately there is little evidence on the impact of RP on health. Where studies are available these assess the impact of the more controversial TRP on health outcomes, which is not a focus of this literature review. Lopez-Casasnovas (2000), proposes that available studies cannot provide conclusive evidence firstly because of the paucity of time series studies at an individual patient level with adequate before and after time periods, and secondly because of the complexity of monitoring concurrent health system changes (Lopez-Casasnovas, 2000).

Identification of gaps / Needs for further research

The cost advantage of increased generic utilisation is undoubted. The European Commission, following publication of its final competition inquiry report encouraged its members to increase market entry and penetration of generics to improve price competition (Usher, Barry 2012).

However, although there are multiple well-documented pro-generic policies, the appropriate mix of these policies to achieve maximum generic penetration and price competition is unclear. Concerns have been raised that generic reference pricing may have a mixed impact on drug price competition, utilisation patterns, health outcomes and innovative drug development, particularly over a longer time period. Until recently, there have been very few studies that focus on the impact of various pro-generic policies in particular there have been few studies that analyse the impact of different combinations of these policies. Although there has been an increase in published studies in the developed world over the past 10 years, many of these studies use aggregate level rather than individual case/patient-level data, due to the lack of accessibility to micro-data. In LMICs, however there are very few published studies of the empirical effect of reference pricing (López-Casasnovas, Puig-Junoy 2000).

A major gap in research is studies of the impact of pro-generic policies, including reference pricing, in LMICs. This is supported by Kaplan who stated: “Evaluations of generic medicines

policies in LMICs are urgently needed” (Kaplan et al. 2012). However in developed nations, research gaps include non-aggregated data, preferably over longer time periods that can address the impact of various combinations of pro-generic policies, in an effort to identify the most appropriate and effective mix to enable implementation of an optimal combination of policies.

References

- Aaserud, M., Austvoll-Dahlgren, A., Kösters, J.P., Oxman, A.D., Ramsay, C. & Sturm, H. 2006, "Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies", *The Cochrane Library*.
- Austvoll-Dahlgren, A., Aaserud, M., Vist, G.E., Ramsay, C., Oxman, A.D., Sturm, H., Kösters, J.P. & Vernby, Å 2008, "Pharmaceutical policies: effects of cap and co-payment on rational drug use", *The Cochrane Library*.
- Bester, M. & Badenhorst, E. 2012, *Medicines Review, 2011*. [Homepage of Mediscor PBM.], [Online]. Available: www.mediscor.net [2014, September 4].
- Brekke, K.R., Konigbauer, I. & Straume, O.R. 2007, "Reference pricing of pharmaceuticals", *Journal of health economics*, vol. 26, pp. 613+.
- Brekke, K.R., Grasdal, A.L. & Holmas, T.H. 2007, *Regulation and Pricing of Pharmaceuticals: Reference Pricing or Price Cap Regulation?*, CESifo GmbH, CESifo Working Paper Series: CESifo Working Paper No. 2059.
- Brekke, K.R., Grasdal, A.L. & Holmas, T.H. 2009, "Regulation and Pricing of Pharmaceuticals: Reference Pricing or Price Cap Regulation?", *European Economic Review*, vol. 53, no. 2, pp. 170-185.
- Brekke, K.R., Holmas, T.H. & Straume, O.R. 2011, "Reference Pricing, Competition, and Pharmaceutical Expenditures: Theory and Evidence from a Natural Experiment", *Journal of Public Economics*, vol. 95, no. 7-8, pp. 624-638.
- British Columbia Ministry of Health 2012, *PharmaCare Policy Manual 2012* [Homepage of British Columbia Province], [Online]. Available: <http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/pharmacare-publications/pharmacare-policy-manual-2012#section-5> [2015, November 9]
- Cameron, A. & Laing, R. 2010, "Cost savings of switching private sector consumption from originator brand medicines to generic equivalents", *World health report*, .
- Chen, C.L., Chen, L. & Yang, W.C. 2008, "The influences of Taiwan's generic grouping price policy on drug prices and expenditures: evidence from analysing the consumption of the three most-used classes of cardiovascular drugs", *BMC public health*, vol. 8, pp. 118-2458-8-118.
- Costa-Fonta, J. & Puig-Junoy, J. 2004, *Regulatory ambivalence and the limitations of pharmaceutical policy in Spain* [Homepage of Econpapers.repec.org], [Online]. Available: <http://www.econ.upf.edu/docs/papers/downloads/762.pdf> [2013, August 12].
- Council for Medical Schemes 2011, *Annual Report 2010-2011*, Council for Medical Schemes.

Council for Medical Schemes 2014, *Annual Report 2013-2014*, Council for Medical Schemes.

Crasto, A.M. 2014, *New drug approvals*. Available: <http://newdrugapprovals.org/south-africa-mcc/> [2014, August 14].

Department of Health 2004, *Medicines and Related Substances Act, 1965; Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances*, Pretoria: Department of Health, Government Gazette 26304, April.

Department of Health 2006, *Medicines and Related Substances Act, 1965; Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances. Determination of Maximum Increase in the Single Exit Price of Medicine and Scheduled Substances for the Period up until 01 July 2007*, Pretoria: Department of Health, Government Gazette 29443, December.

Department of Health 2008a, *Medicines and Related Substances Act, 1965; Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances. Determination of Maximum Increase in the Single Exit Price of Medicine and Scheduled Substances for the Period up until 30 September 2009*, Pretoria: Department of Health, Government Gazette 31735, December.

Department of Health 2008b, *Medicines and Related Substances Act, 1965; Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances. Determination of Maximum Increase in the Single Exit Price of Medicine and Scheduled Substances for the Period up until 31 July 2008*, Pretoria: Department of Health, Government Gazette 30901, March.

Department of Health 2010a, *Medicines and Related Substances Act, 1965; Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances: (Methodology for International Benchmarking of Prices of Medicines and Scheduled Substances in South Africa)*. Pretoria: Department of Health, Government Gazette 9941.

Department of Health 2010b, *Medicines and Related Substances Act, 1965. Determination of Maximum Increase in the Single Exit Price of Medicine and Scheduled Substances for 2010*, Pretoria: Department of Health, Government Gazette 33034, March.

Department of Health 2011, *Medicines and Related Substances Act, 1965; Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances: Amendment (Single Exist Price adjustment for the Year 2011*, Pretoria: Department of Health, Government Gazette 33961, January.

Department of Health 2013, *Medicines and Related Substances Act, 1965; Annual adjustment of Single Exit Price for Medicines and Scheduled Substances for the Year 2013*, Pretoria: Department of Health, Government Gazette 36087, January.

Department of Health 2014, *Medicines and Related Substances Act, 1965. Regulations relating to a transparent pricing system for medicines and scheduled substances: (Benchmark Methodology)*, Pretoria: Department of Health, Government Gazette 37625, May.

- Department of Trade and Industry 2013, *Draft National Policy on Intellectual Property, 2013*, Department of Trade and Industry, Government Gazette Notice 918 of 2013.
- Deroukakis, M. 2007, "Mandatory substitution successful: original article", *South African Medical Journal*, vol. 97, no. 1, pp. 63-64.
- Dunne, S., Shannon, B., Dunne, C. & Cullen, W. 2013, "A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study", *BMC Pharmacology & Toxicology*, vol. 14, pp. 1-1.
- Dylst, P., Vulto, A. & Simoens, S. 2011, "The impact of reference-pricing systems in Europe: a literature review and case studies", *Expert Review Of Pharmacoeconomics & Outcomes Research*, vol. 11, no. 6, pp. 729-737.
- European Commission 2009, *Pharmaceutical Sector Inquiry. Final Report*. Available: <http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/> [2011, September 5].
- Faden, L., Vialle-Valentin, C., Ross-Degnan, D. & Wagner, A. 2011, *WHO/HAI Project on Medicine Prices and Availability. Review Series on Pharmaceutical Pricing Policies and Interventions. Working Paper 2: The Role of Health Insurance in the Cost-Effective Use of Medicines*, Drug Policy Research Group and WHO Collaborating Center in Pharmaceutical Policy. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute.
- Federal Trade Commission 2011, "Authorized generic drugs: short-term effects and long-term impact", *Retrieved September*, vol. 10, pp. 2014.
- Fiorio, C.V. & Siciliani, L. 2010, "Co-payments and the demand for pharmaceuticals: evidence from Italy", *Economic Modelling*, vol. 27, no. 4, pp. 835-841.
- Galizzi, M.M., Ghislandi, S. & Miraldo, M. 2011, "Effects of reference pricing in pharmaceutical markets: a review", *PharmacoEconomics*, vol. 29, no. 1, pp. 17-33.
- Ghislandi, S., Krulichova, I. & Garattini, L. 2005, "Pharmaceutical policy in Italy: towards a structural change?", *Health policy (Amsterdam, Netherlands)*, vol. 72, no. 1, pp. 53-63.
- Golob, U., Molj, B. & Podnar, K. 2007, "How reference pricing for pharmaceuticals can increase generic share of market: the Slovenian experience", *Journal of Public Policy and Marketing*, vol. 26, no. 1, pp. 89+.
- Hawkins, L. 2011, *WHO/HAI project on medicine prices and availability: Review series on pharmaceutical pricing policies and interventions: Working paper 4: Competition Policy*, World Health Organisation, Geneva.
- Intercontinental Marketing Services [IMS] 2012, *Responsible use of Medicines*. Available: <http://www.imshealth.com/portal/site/imshealth/menuitem.762a961826aad98f53c753c7>

[1ad8c22a/?vgnextoid=faf9ee0a8e631410VgnVCM10000076192ca2RCRD&vgnnextfmt=defa](#)
[ult](#) [2014, September 4].

Kanavos, P., Costa-Font, J. & Seeley, E. 2008, "Competition in off-patent drug markets: Issues, regulation and evidence", *Economic Policy*, vol. 23, no. 55, pp. 500-544.

Kaplan, W.A., Ritz, L.S., Vitello, M. & Wirtz, V.J. 2012, "Policies to promote use of generic medicines in low and middle income countries: A review of published literature, 2000-2010", *Health Policy*, vol. 106, no. 3, pp. 211-224.

Leopold, C., Mantel-Teeuwisse, A.K., Seyfang, L., Vogler S., de Joncheere, K., Laing, R.L., Leufkens, H. 2012, "Impact of External Price Referencing on Medicine Prices – A Price Comparison Among 14 European Countries", *South Med Review*, vol. 5, no. 2, pp. 34–41.

López-Casasnovas, G. & Puig-Junoy, J. 2000, "Review of the literature on reference pricing", *Health policy*, vol. 54, no. 2, pp. 87-123.

Magazzini, L., Pammolli, F. & Riccaboni, M. 2004, "Dynamic Competition in Pharmaceuticals: Patent Expiry, Generic Penetration, and Industry Structure", *European Journal of Health Economics*, vol. 5, no. 2, pp. 175-182.

Miraldo, M. 2009, "Reference pricing and firms' pricing strategies", *Journal of health economics*, vol. 28, no. 1, pp. 176-197.

Moran, M. 2010, *Proposed model for reference pricing and generic substitution* [Homepage of Irish Department of Health], [Online]. Available:
<http://health.gov.ie/blog/publications/proposed-model-for-reference-pricing-and-generic-substitution/> [2014, September 12].

Moreno-Torres, I., Puig-Junoy, J. & Borrell, J. 2009, "Generic Entry into the Regulated Spanish Pharmaceutical Market", *Review of Industrial Organization*, vol. 34, no. 4, pp. 373-388.

Mossialos, E., Mrazek, M. & Walley, T. 2004, *Regulating Pharmaceuticals In Europe: Striving For Efficiency, Equity And Quality: Striving for Efficiency, Equity and Quality*, McGraw-Hill International.

Organisation for Economic Co-operation and Development (OECD) 2008, *Pharmaceutical Pricing Policies in a Global Market*, OECD Health Policy Studies.

Puig-Junoy, J. 2005, "What is required to evaluate the impact of pharmaceutical reference pricing?", *Applied Health Economics and Health Policy*, vol. 4, pp. 87+.

Puig-Junoy, J. 2007, "The impact of generic reference pricing interventions in the statin market", *Health policy*, vol. 84, pp. 14+.

Puig-Junoy, J. 2010, "Impact of European pharmaceutical price regulation on generic price competition: a review", *PharmacoEconomics*, vol. 28, no. 8, pp. 649-663.

- Puig-Junoy, J. & Moreno-Torres, I. 2010, "Do generic firms and the Spanish public purchaser respond to consumer price differences of generics under reference pricing?", *Health Policy*, vol. 98, no. 2-3, pp. 186-194.
- Puig-Junoy, J. 2012, "Do higher-priced generic medicines enjoy a competitive advantage under reference pricing?", *Applied Health Economics And Health Policy*, vol. 10, no. 6, pp. 441-451.
- Rothberg, A.D., Blignault, J., Serfontein, C.B., Valodia, B., Eekhout, S. & Pels, L.M. 2004, "Experience of a medicines reference-pricing model", *South African Medical Journal*, vol. 94, no. 3, pp. 183-188.
- Simoens, S. 2012, "A review of generic medicine pricing in Europe", *GaBI J*, vol. 1, no. 1, pp. 8-12.
- Simoens, S., De Bruyn, K., Bogaert, M. & Laekeman, G. 2005, "Pharmaceutical policy regarding generic drugs in Belgium", *PharmacoEconomics*, vol. 23, no. 8, pp. 755-766.
- Usher, C. & Barry, M. 2012, "A reference pricing system for Ireland", *Expert Rev Pharmacoecon Outcomes Res*, vol. 12, no. 6, pp. 675.
- von der Schulenburg, F., Vondoros, S. & Kanavos, P. 2011, "The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors", *Health Economics Review*, vol. 1, no. 1, pp. 18-18.
- World Health Organisation 2000, *A Quick Reference Compendium of Selected Key Terms used in The World Health Report 2000 issued by the World Health Organisation*. . Available: http://www.who.int/health-systems-performance/docs/glossary.htm#outofpocket_payments [2011, October 9].
- World Health Organisation 2014a, *ATC/DDD Index*. Available: http://www.whocc.no/atc_ddd_index/ [2014, September 12].
- World Health Organisation 2014b, *Generic Drugs*. [Homepage of World Health Organisation], [Online]. Available: <http://www.who.int/trade/glossary/story034/en/index.html> [2014, June 26].

Part C:

Journal manuscript

An Analysis of the Impact of Generic Medicine Reference Pricing in a Sector of the South African Private Healthcare Insurance Industry

Jennifer Noble-Luckhoff¹

Affiliations ¹ Health Economics Unit, University of Cape Town, Anzio Road, Observatory, Cape Town, South Africa

Corresponding Author J. Noble-Luckhoff

Contact details

Address: PO Box 38632
Pinelands
Cape Town, 7430

Telephone: +27 83 443 1110 (mobile)
+27 21 794021 (home)
+27 21 466 3311 (work)

Email: jennin@medscheme.co.za, or noble.jenni@gmail.com

Acknowledgements I would like to acknowledge the following people who have assisted me over the course of this study:

- Prof Diane McIntyre my supervisor at the Health Economics Unit, University of Cape Town
- MediKredit Pty (Ltd) for funding 2 years of my MPH studies and for enabling access to data used in this dissertation
- Yvette van der Westhuizen, of MediKredit for assisting me with data extraction
- Medscheme Holdings Pty (Ltd) for funding 1 year of my studies, and for allowing me access to actuarial and statistician resources to assist me in analyses
- Lourens Wepener of Medscheme Holdings for assisting me with data analysis.

Conflict of Interest:

- I was an employee at MediKredit Pty (Ltd) until June 2012, over the period where I initiated this study. This study is based on MediKredit's generic reference pricing product, MMAP®
- I have since moved to Medscheme Holdings Pty (Ltd), which has its own generic reference pricing product, MPL®.

Abstract

Objectives

To determine the impact of generic reference pricing in a privately-insured healthcare setting in South Africa, a low and middle income country. Results were compared with international empirical data in an effort to draw policy conclusions on how to increase generic utilisation in this setting.

Methods

A time-series intervention study was conducted on retrospective records data to which generic medicine pricing had applied. The impact of reference pricing on drug price, expenditure, market share and out-of-pocket payments was determined for two categories, Clopidogrel and Desloratadine. Clopidogrel has an authorised generic.

Results

The overall medicine expenditure decreased across both categories. Generic prices decreased but originator prices were not impacted. The originators rapidly lost market share, declining to almost 4% for Clopidogrel and 22% for Desloratadine. Clopidogrel's authorised generic gained 68% of the market despite being priced above the reference price and generating increasing co-payments. For Desloratadine generics gained greater market share (80%). Across both categories there was minimal change in overall expenditure on out-of-pocket payments.

Conclusions

The impact of generic reference pricing in this setting is mostly consistent with international literature. This study highlights the negative impact that brand loyalty and information asymmetry have on pro-generic policies, and how originator marketing strategies use these factors to their advantage. It supports the need to align incentives of stakeholders in the demand side chain through the adoption of a multi-pronged pro-generic approach.

Highlights

- The impact of generic reference pricing in this study is mostly consistent with literature
- Authorised generics gained market dominance, despite above-reference prices and increasing out-of-pocket payments
- Originator companies' marketing strategies effectively reduce the impact of generics
- Pro-generic policies must include focus on the demand-side chain to be effective

Key words

Generic medicines

Pharmaceutical policy

Low and middle income countries

Reference pricing

Introduction

Pharmaceutical expenditure is responsible for a substantial percentage of the total cost of health care and increases in pharmaceutical expenditure continue to exceed economic growth and inflation (1). Generic medicines play an important role in limiting this expenditure, and consequently there is an international drive to increase their utilisation. Intercontinental Marketing Services (IMS) estimated that between 19 and 40 billion US dollars could be saved worldwide through increased use of safe, low-cost generics (2).

Multiple pro-generic policies have been implemented particularly in high income countries. These policies include demand and supply-side policies that aim to encourage generic entry and generic competition by influencing the reimbursement of medicines, the market price of medicines and/or the regulation of market authorisation (3). One such policy is generic medicine reference pricing (GRP). GRP sets a fixed maximum reimbursement amount for clusters of bio-equivalent drugs, without placing any restrictions on the manufacturers' price (1,4). GRP has been implemented in many OECD countries, specifically in Europe (5).

Expected profits, determined by patent protection policies, the extent of price regulation and price competition, are thought to impact the entry and penetration of a generic to a market (6,7). 'First mover advantages' (which encourage the launch of generic drugs by allowing a market exclusivity period), non-transparent discounting, other demand-side incentives as well as originator drug marketing strategies (8) also impact generic market entry.

Strategies used by originator companies to delay or minimize the increasing market share of generic drugs include 'authorised generics'. 'Authorised generics' (AGs), also referred to as 'clones', 'auto-generics' or 'co-marketed copies' are "pharmaceutical products that are approved as brand-name drugs but marketed as generic drugs" (9). They are manufactured either by the originator company or by another pharmaceutical manufacturer through acquisition or joint venture, and may be launched prior to the originator's patent expiry. This is based on the concept of the 'first-mover advantage' in which the first generic launched is able to gain substantial market share at a higher price than that of later generics. As the quality of the AG is perceived to be higher than that of later entrants, first entrant prices can be maintained at a higher level; the products may retain market share for a longer period of time (10).

In South Africa the registration and price of medicines is highly regulated, with few pro-generic policies in place to encourage market entry. Registration requires proof of bioequivalence of generic medicines. Although it is reported that the registration of generic products is faster than that of originator products (11), there is no specific policy for the fast-tracking of regulatory approval of generic medication, and first mover advantages are not applied. Registration does however apply the Bolar provision, a pro-generic regulatory policy which allows generic companies to complete regulatory requirements including bioequivalence studies before an originator's patent has expired. A change in South Africa's Patent Act was proposed in 2013 to incorporate the TRIPS Agreement 'patent flexibilities', including compulsory licensing, which allows a third party to produce the patented product or process without the consent of the patent owner (12). This regulatory change has however been highly contentious and has not yet been promulgated.

Medicine prices have been regulated since 2004, with the implementation of the Single Exit Price (SEP) for scheduled medicines. The SEP includes the logistics fee which may be negotiated between the manufacturer and logistics providers/distributors. Manufacturers or importers of medicines are obliged to sell scheduled medicine at the same price to all purchasers with the exception of government, where a tender system applies. There is, however, no regulation limiting generic prices relative to the originator price. Simultaneously rebates, discounts and other incentive schemes offered by manufacturers were prohibited and dispensing fees were regulated, however the dispensing fees were legally contested and only implemented in 2010. Although the regulated maximum dispensing fee involves a higher percentage on lower cost items, the dispensing fee for lower cost items is less in absolute terms than that of higher cost items and thus the fee is unlikely to be pro-generic.

There are no specific pro-generic pricing or reimbursement policies implemented at a national level, including GRP. The only national pro-generic demand side policy is mandatory generic substitution which requires patients to be informed of the availability of 'interchangeable multi-source medicine' (generic) alternatives at the time of dispensing. However in the private insurance industry generic reference pricing systems are widely implemented. The first system, called the "Maximum Medical Aid Price" (MMAP), was implemented in 1987, and was the industry standard for many years. Subsequently multiple different GRP models have been implemented by various administrators of medical insurance companies.

Numerous studies have been conducted internationally to analyse the impact of pro-generic policies, including GRP. However, what is not well established is the impact of GRP in low-to-middle income countries (LMICs) (13,14), and whether it is comparable to the impact in high income countries. A review of published studies on the impact of pro-generic policy in LMICs by Kaplan *et al.* found only one study in a 10-year period (January 2000 to March 2010) that assesses the impact of generic reference pricing (14). This study reviews the impact of reference pricing on product prices and on expenditure but does not analyse the impact on utilisation, either at an aggregate or patient level (15).

The objective of this article is to address this gap in research by analysing the impact of GRP on product price, expenditure, utilisation and out-of-pocket (OOP) payments in a sector of South Africa's private health insurance industry, using robust claim level data. The results are analysed against the background of the existing medicine policies applicable to this sector, as these may have an impact on generic market entry and penetration.

Methods

Study design

The study is a time series intervention study analyzing the impact of a GRP model using retrospective patient-level secondary data obtained through records review.

Sampling strategy

The 'Maximum Medical Aid Price' (MMAP) model is the GRP model that is evaluated. This model is applied to a sector of privately insured population in South Africa. Criteria for selection of GRP categories include categories with comparatively high volume of claims that were newly implemented between April 2008 and July 2009. Data prior to 2008 was not available. The time period was limited in order to maximize the post-implementation analysis period to at least 4 years. Any category that was withdrawn either temporarily or permanently during this period was excluded.

The sample population includes members of medical insurance companies that applied MMAP consistently over the analysis period, but did not apply other managed care policies that may act as a confounder, such as therapeutic reference pricing (TRP), formularies and benefit exclusions.

Insurers that had a membership variation greater than 20% over the study period were also excluded.

Outcomes measured

The impact of GRP on variables of drug price, drug expenditure, market share and out-of-pocket payment on drugs within the GRP cluster is measured.

Data analysis

A time-series analysis of the data is conducted. The 'periods' of analysis are the time intervals 4 months prior to the implementation of GRP (MMAPI launch date), and the time intervals between subsequent GRP price changes. These time intervals vary substantially in duration because of the GRP price change dates are not consistent. In each case the impact of GRP is measured by analyzing changes in the originator, the AG (where applicable) and other generic drugs. All monetary figures are presented in nominal terms. Within each period the reference price remains fixed but the price of individual drugs within each cluster may change.

The impact of the implementation of GRP on the price of products in that cluster is determined by comparing the product prices to the GRP for that period.

Drug expenditure is analysed by comparing the expenditure per day and the expenditure per Defined Daily Dose (DDD) for that GRP category. DDD is defined as 'the assumed average maintenance dose per day for a drug used for its main indication in adults' (16). Drug expenditure is reported 'per day' to ensure a comparable denominator as the period intervals are not consistent. Expenditure per day is a function of price and utilisation, whereas expenditure per DDD takes into account the variation in product price, while controlling for volume changes.

Market share by volume and value is analysed by comparing the percentage of DDDs and expenditure respectively. Out-of-pocket payment is assessed by determining the percentage of DDDs that generate an OOP payment (DDD with OOP payment as a % of total DDDs), the percentage of total drug expenditure paid out-of-pocket (OOP expenditure as % Total Expenditure) and changes in the OOP value per DDD.

Results

Sample population and GRP categories

A mean of 107,407 insured lives (SD = 1,194) from 4 different insurers met the inclusion criteria. All 4 insurers have restricted membership. Many insurers were eliminated due to their application of benefit exclusions, drug formularies, membership variability and or therapeutic reference pricing, all of which act as confounders.

Two GRP categories, Desloratadine and Clopidogrel, met the inclusion criteria. Desloratadine, an antihistamine (ATC: R06AX27), is used to treat acute and chronic conditions, whereas Clopidogrel, a platelet aggregation inhibitor (ATC: B01AC04), is typically used on a chronic basis to prevent thrombosis. The period of analysis is 4.5 years (1635 days) for Clopidogrel and 5.2 years (1891 days) for Desloratadine (See Table A in Online Appendix for further details). Over the study period there were 7 GRP price changes for Clopidogrel and 8 GRP price changes for Desloratadine following GRP implementation, occurring at varying intervals. These determine the analysis periods (See Table B in Online Appendix for further detail). An AG was launched for Clopidogrel but not for Desloratadine. Five generics were launched for Clopidogrel, four of which were launched within one year of the AG, and 4 for Desloratadine, launched over a period of 3 years.

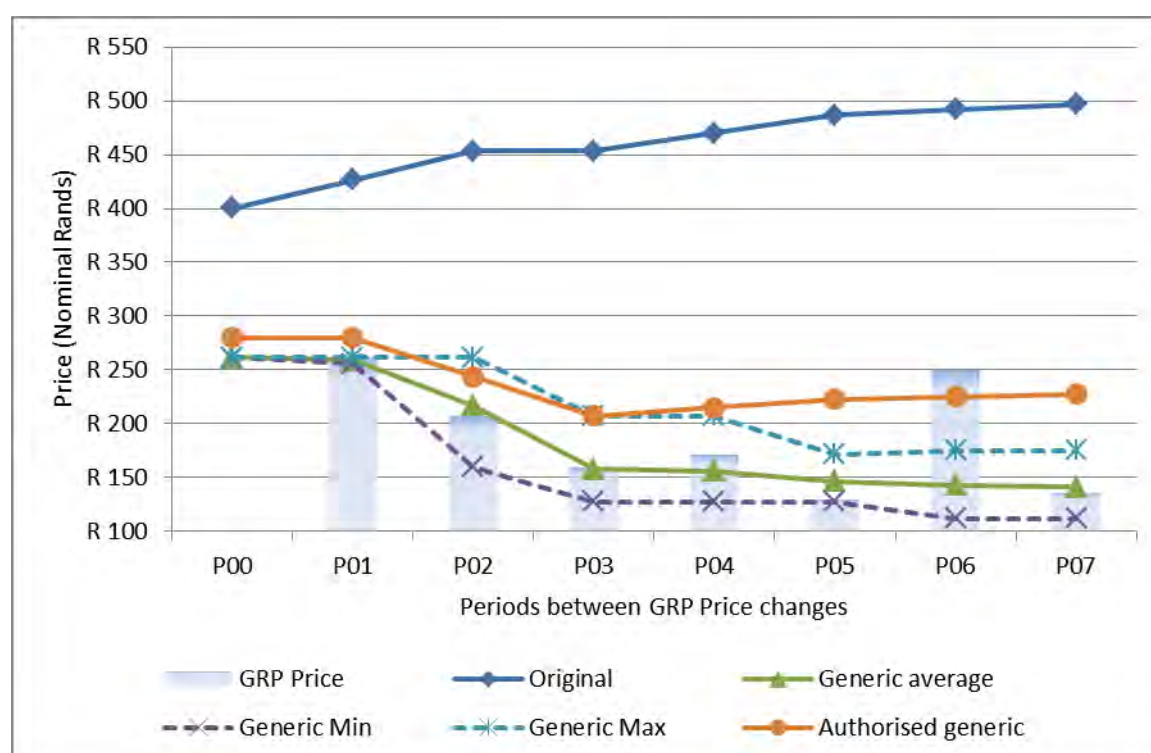
Impact on price

Originator: GRP had no impact on the originator price of either category – these products' prices continued to increase in line with the legislated single exit price (SEP) increase (see Figure 1). When GRP was first implemented the originator price for Clopidogrel and Desloratadine was 63% and 34% (respectively) higher than GRP; at the end of the study period the originator was 268% and 86% (respectively) higher than GRP.

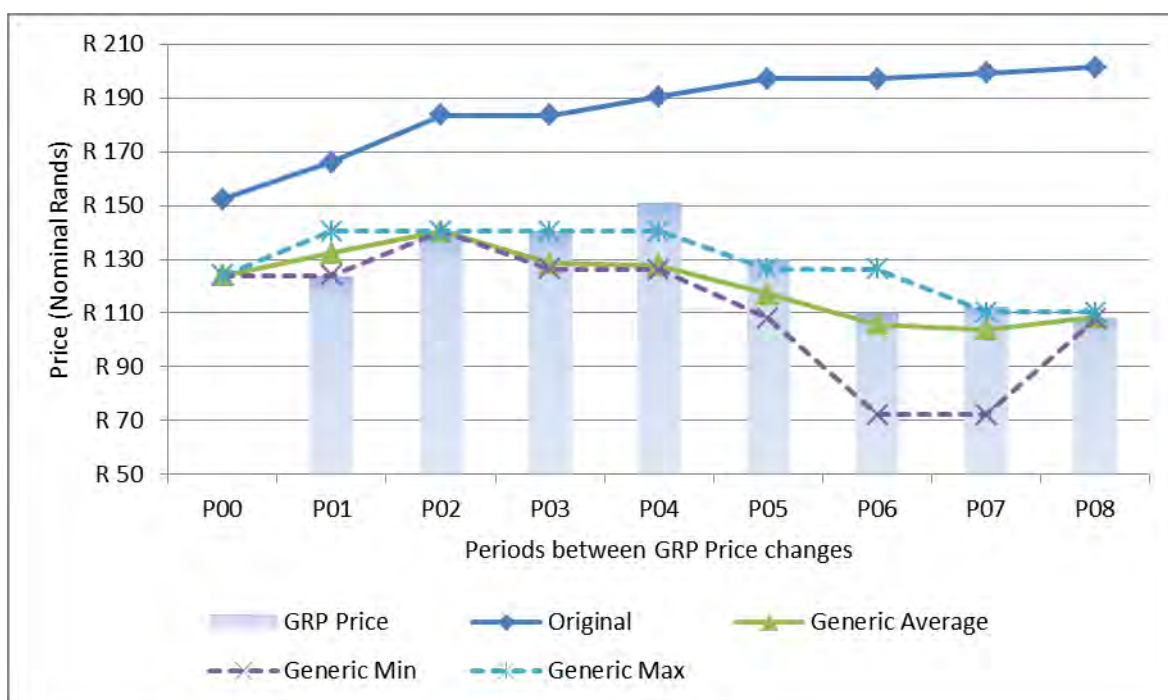
Authorised Generic: Clopidogrel's AG launched at a 30% reduction of the originator's price. It reduced by a further 35% to match GRP once the 3rd generic was launched and thereafter it continued to increase by the allowed annual SEP increase, irrespective of any GRP changes. At the end of the study period the AG's price was 69% higher than that of GRP. No AG was launched for Desloratadine.

Generics: For both Clopidogrel and Desloratadine GRP was implemented at the same price of the initial generics, shortly after their launch. Clopidogrel's first generic launched 2 days after the AG and the second generic launched almost 3 weeks later. All new generics launched at a price lower or equal to the lowest-priced generic at the time. Changes in the GRP largely appear to follow the change in price of a generic in the cluster; however in most instances once the reference price is set other generics tend to align at or below the GRP. On some occasions an existing generic decreased its price in response to a new generic entrant's lower price, despite being below the GRP. The GRP of Clopidogrel at the end of the study period was 5% more than the average price of all generics, with the lowest priced product 17% less than GRP and 344% less than the originator; the highest price product was 30% more than GRP and 185% less than the originator. For Desloratadine the GRP at the end of the study was the same as the average generic price and 82% lower than the originator price.

It should be noted that for Clopidogrel the GRP increased substantially in the 6th time period after GRP implementation. This was due to a shortage of generic stock at the time, prompting the GRP to be set above the AG's price so as not to negatively impact patients with OOP payments.



1 a) Clopidogrel price changes (Nominal)



1 b) Desloratadine price changes (Nominal)

Figure 1: Impact of GRP on prices of Clopidogrel and Desloratadine products over the study period

Impact on expenditure, volumes and market share

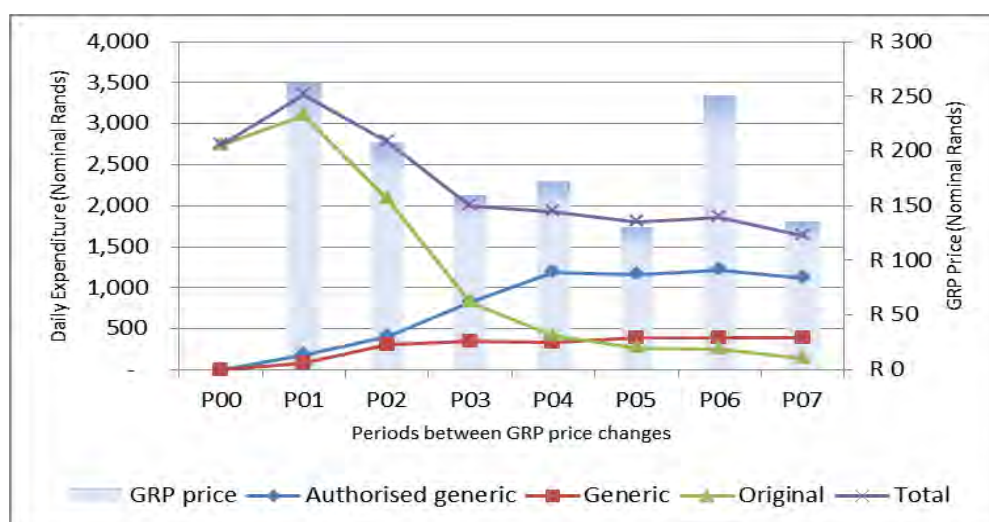
Clopidogrel

The **overall** expenditure per day for the Clopidogrel category increased by 23% in the first period after GRP implementation, attributed to a 26% increase in DDDs/day and countered by a 3% decrease in expenditure/DDD (see Figure 2). Following this initial increase, overall expenditure per day and expenditure/DDD decreased over the remainder of the study period, while there were only small fluctuations in utilisation. From the pre-GRP implementation to the end of the study period the overall expenditure per day decreased by 40%, despite a 13% increase in the DDDs/day. The overall expenditure/DDD decreased by 47% over the same period.

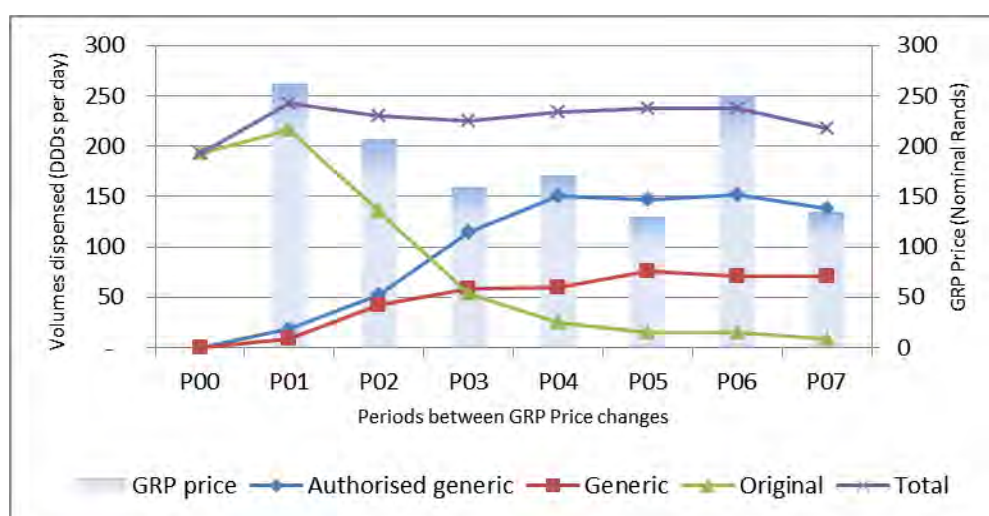
As indicated in Figure 2, following an initial 13% increase, the daily dispensed volume of the originator decreased substantially (by 96%) over the study period following the implementation of GRP, resulting in a similar decrease in expenditure per day. However the cost per DDD increased by 21%, mirroring the corresponding increase in the price of the originator. The market

share of the originator plummeted to 4% by volume and 9% by value over the corresponding period (see Figure A in Online Appendix).

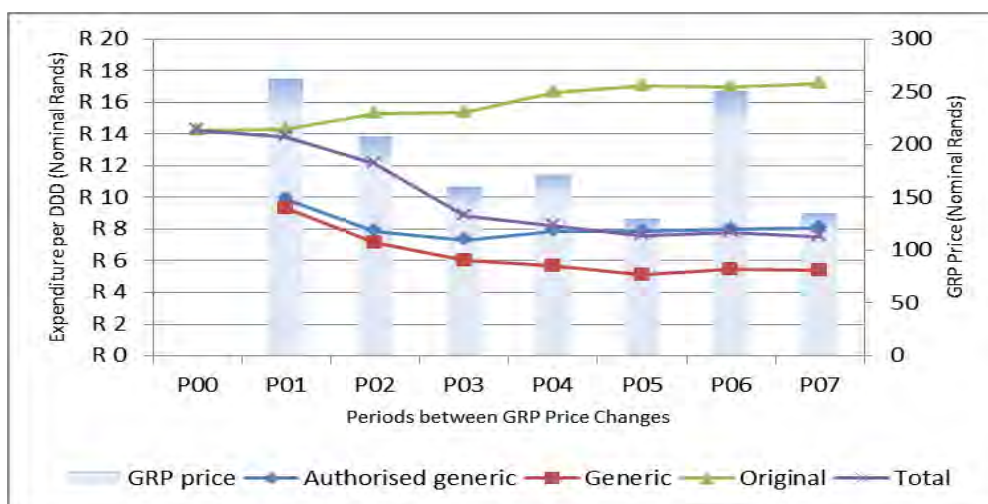
Clopidogrel's AG increased dramatically in daily volumes dispensed (by 724%) and daily expenditure (555% increase) over the first four periods, capturing 61% and 64% of the market share by value and volume respectively. Over this time the cost per DDD decreased by 20%, in line with the 23% decrease in the AG's price. However, from this point onwards the AG's price started to increase and the dispensed volumes and expenditure stabilized. Despite this levelling off, the AG's majority market share by volume was maintained, increasing slightly by expenditure in light of the increased product price.



2a) Variation in expenditure per day (Nominal)



2b) Variation in volume dispensed (Defined Daily Dose per day)



2c) Variation in expenditure per DDD (Nominal)

Figure 2: Impact of GRP on Clopidogrel products over the study period

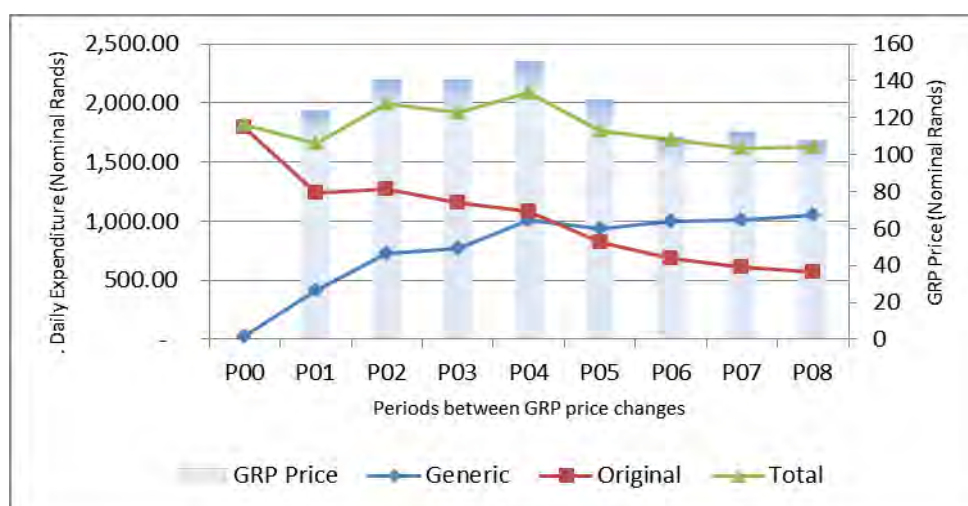
Similar to the AG, Clopidogrel's **generics** increased dramatically in expenditure and dispensed volume in the two periods immediately after GRP implementation. However, when compared to the rapid increase (190%) in the utilisation of the AG over the next 2 periods, the increase in generics utilisation tailed off to 41% (see Figure 2). Although the generics gained a substantial increase in market share over the study period, capturing 25% of dispensed volumes in the first four periods following GRP implementation, they continuously trailed behind the AG's market share. By the end of the study the generics held almost one third of the market by volume and almost a quarter of the market's total value, whereas the AG held more than two thirds by value and 63% by volume (see Figure A in Online Appendix).

Desloratadine

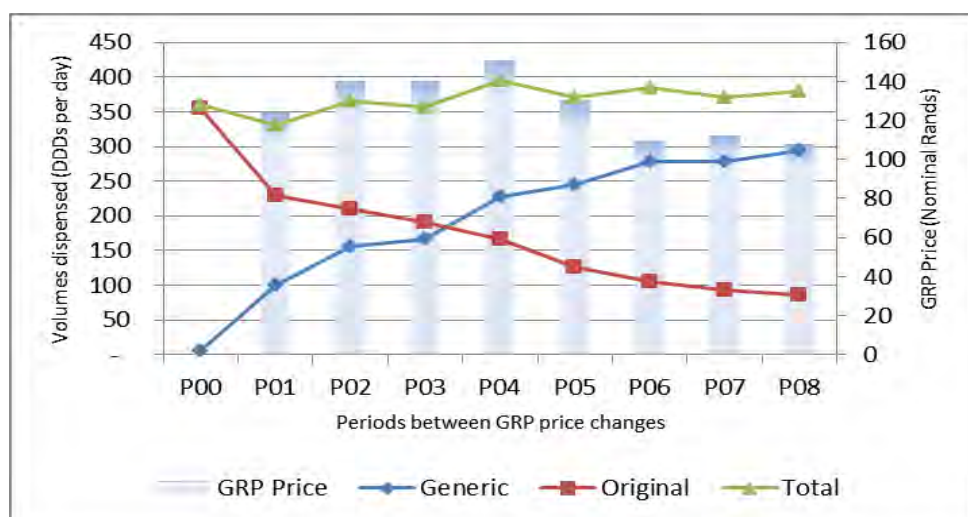
GRP was implemented 12 weeks after the launch of the first Desloratadine generic. In this pre-implementation period, very low generic volumes were dispensed. However, following the implementation of GRP the generic volumes and associated expenditure increased rapidly especially in the 4 periods (2.4 years) following implementation, with an overall increase of 4297% and 4084% respectively (see Figure 3). The expenditure per DDD, however, decreased by 13% over the study period, which correlates with the 13% reduction in average generic price. In contrast the originator's daily volumes and expenditure decreased by 76% and 68% respectively over the study period, while its expenditure per DDD increased by 31%. The greatest impact was again in the 4 periods after GRP implementation. Across the Desloratadine category for the

duration of the study there was a 15% increase in daily volumes, a 10% decrease in daily expenditure and a 15% decrease in average expenditure per DDD following GRP implementation.

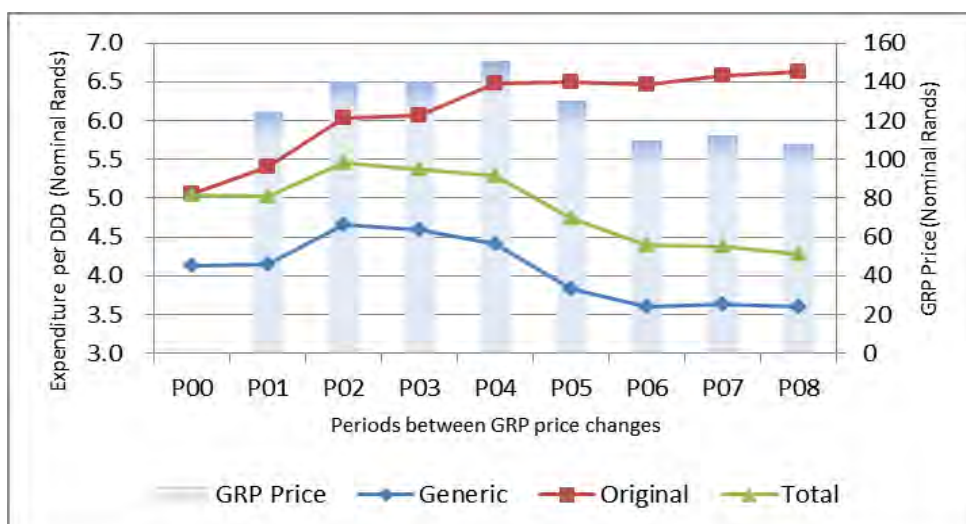
The generic market share increased continuously over the study period to gain 77% of the volume dispensed and 63% of expenditure. The originator's market share declined to 23% by volume and 36% by value (see Figure B in Online Appendix).



3a) Variation in expenditure per day (Nominal)



3b) Variation in volume dispensed (Defined Daily Dose per day)



3c) Variation in expenditure per DDD (Nominal)

Figure 3: Impact of GRP on Desloratadine products over the study period

Impact on out-of-pocket payments

Clopidogrel

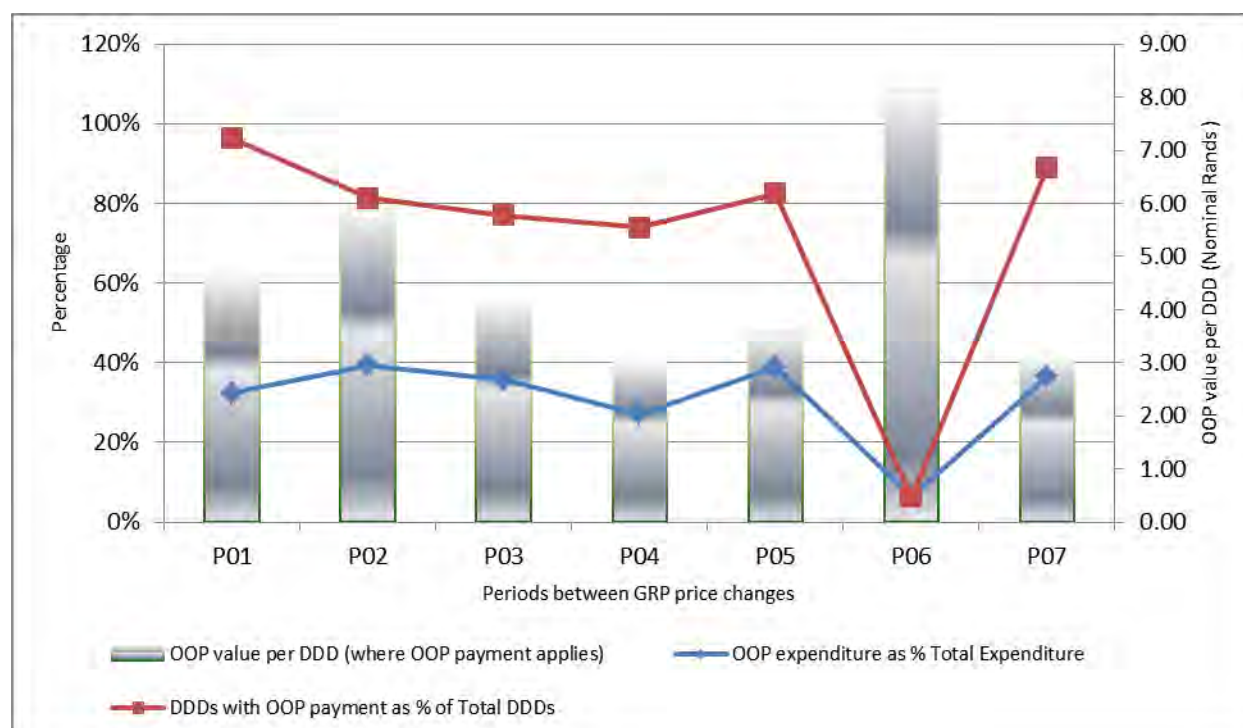
As indicated in Figure 4, when GRP was first implemented 96% of all dispensed Clopidogrel was subject to an OOP payment. Subsequent fluctuations in the GRP resulted in inconsistent changes in the volumes of Clopidogrel that attracted OOP payments, particularly when the GRP was adjusted above the AG price in the 6th period due to a shortage of generic supply. By the end of the study the volume of Clopidogrel with an OOP payment was approximately 89%. The percentage of total drug expenditure that was paid out-of-pocket increased from 33% to 36% from the start to the end of the study. The OOP payment value per DDD, where applied, decreased by 34% over the corresponding period.

The OOP payment trends for the AG are however opposite to that of the overall category. As a percentage of total the AG's OOP expenditure and DDDs subject to a co-payment increased consistently across the study period. At the end of the study more than two-thirds of the market was willing-to-pay out-of-pocket for the AG, despite a dramatic increase in the quantum of the OOP payment (from 6% to 42% of the total drug cost) over the study period (see Figure 4a).

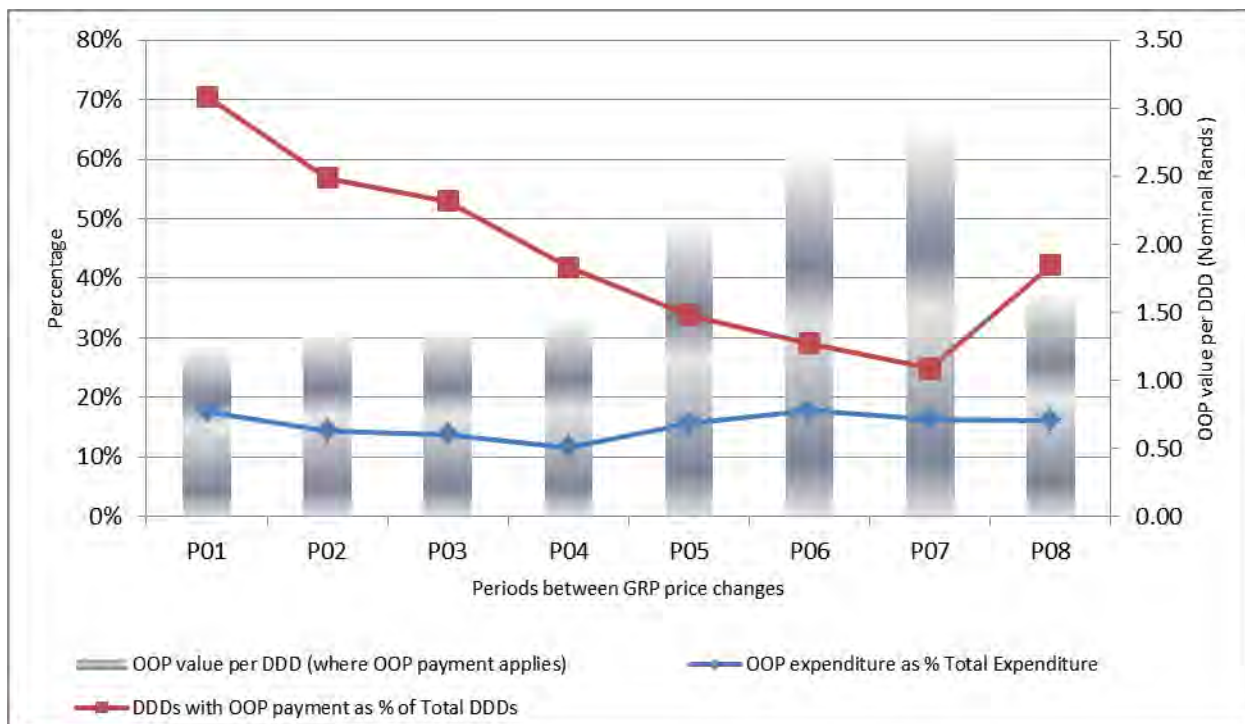
Desloratadine

The percentage of Desloratadine that was subject to an out-of-pocket payment reduced more dramatically than for Clopidogrel following implementation of GRP. At the start of the study 70%

of Desloratadine was subject to a co-payment, but reduced to 42% at the end of the study. There was a less pronounced decrease in the % of total expenditure that was paid out-of-pocket, as indicated in Figure 4. However, where an out-of-pocket payment was due, this was seen to increase in value by 31% from the start to end of the study period. The increase in the quantum of the OOP payment and the percentage of dispensed Desloratadine with an OOP payment as seen in the 8th period (P08) in Figure 4b, was due to the lowest cost generic increasing its price to the GRP level.



4 a) Clopidogrel



4 b) Desloratadine

Figure 4: Impact of GRP on out-of-pocket payments

Discussion

The overall effect of the GRP model studied supports available literature in that it is seen to have a striking initial impact on price, expenditure and market share. Substantial decreases in the originator's market share and expenditure are contrasted by increases in generic market share and expenditure, with a nett effect of an increase in total volumes but decrease in expenditure. In keeping with other studies this impact stabilizes over the long-term (8,10,17-19). In this analysis the initial impact is seen over a period of 1.5 – 2.5 years, longer than the few months reported in another study (19), after which it appears to reach saturation point, with only minimal changes thereafter. Similar findings in Norway prompted the country to withdraw GRP 8 years after implementation, citing that GRP resulted in insufficient long-term savings (17). In this analysis, however, a transient *increase* in total expenditure and volume is seen in both RP categories following the initial implementation of GRP. This may be attributed to increased access to reduced-price generics and AG, not yet offset by the decrease in volumes of the originator. Several studies have shown a decrease in demand with the implementation of cost-sharing policies. An Italian study based on a natural experiment showed a 4% reduction in per

capita volumes prescribed and a 3.4% reduction in public expenditure with a 1 Euro increase in a fixed co-payment. Similarly a 1 Euro reduction in co-payment resulted in an increase in per capita prescribed volumes and expenditure of 3.4% and 4.9% respectively (20).

This study demonstrates a generalised decrease in the overall price of products within each cluster, also reported in other studies (8,10,18). However, pro-generic effectiveness appears to be limited for originator product prices. The findings of this study support the 'generics paradox' effect, as the originator price of both clusters is seen to be independent of generic competition (8,10,19,21), increasing by the permitted Single Exit Price increase, irrespective of the GRP changes. Factors that may influence originator companies' approach to pricing of originators post generic entry include the introduction of auto-generics which may protect the firm's market share, the concept of brand loyalty to the originator, with the expectation that the prescriber will continue to use the originator, and the risk of parallel importation of lower-priced originator drugs into markets. This generic paradox is in contrast to theoretical studies and Galizzi and Puig-Junoy's findings that drugs above the GRP decrease to the RP level (18,22). In addition, unlike Puig-Junoy's findings (22), there isn't conclusive data supporting the attribution of generic price decrease directly to GRP – the competition of lower-priced generics does impact existing generic prices. This may be due to the GRP pricing methodology, which considers the reliability of generic drug supply and as such does not necessarily use the lowest-priced generic as the reference price. Pricing regulation also has an impact as it appears to induce the 'ratchet effect' whereby some generics increase by the maximum permitted price increase to a level higher than would be expected without pricing regulation (8); however as interim price reductions are allowed in the South African SEP context, prices of some generics are reduced after taking the permitted increase in order to remain competitive.

Of particular interest are the findings related to Clopidogrel's AG, launched as a marketing strategy by the originator to minimise the impact of generic entry. Its market share by volume and value increased rapidly, stabilising higher than the market share of all the generics combined. Because the launch of the first generic was only 2 days after the AG's launch, the AG's market dominance is not thought to be due to a 'first mover advantage'. This dominance is also surprising as the AG's price is consistently higher than GRP *and* generic drug prices. This finding is not in keeping with the Federal Trade Commission's analysis of AGs which found no evidence that the price of AGs was higher than the other generics (9). Use of the AG results in patient OOP

payments which increase as the price differential between the AG price and RP increases. GRP appears to have had no impact on this drug.

This highlights the fact that there are other influencing factors at play and that the pro-generic effectiveness of GRP depends on its success at impacting demand-side measures in addition to the obvious supply-side measures. Demand-side policies may be financial or non-financial and may be directed at prescribers, dispensers and/or patients (8).

GRP does have a demand-side impact on patients through the application of OOP payments. However, the success of this intervention is linked to the patient's willingness-to-pay and the degree of information asymmetry. In the case of Clopidogrel, GRP's lack of impact is evidenced by the AG's majority market share despite more than two-thirds of patients paying an increasing amount out-of-pocket for the AG. It is not possible to determine whether this willingness-to-pay is as a result of price insensitivity (being privately insured patients) and/or due to other factors such as provider and dispenser resistance to switch to generics or managed care protocols limiting access to specific medication together with information asymmetry.

Non-financial interventions that are associated with a positive impact on generic penetration include prescribing by International Non-proprietary Name (INN) (8,23), the use of computerized on-line price and prescribing/dispensing information, monitoring of prescribing behaviour (21) and audits (8). Prescribing by INN is attributed as a key driver in achieving an 83% generic utilisation rates in the United Kingdom in 2009/2010 (23).

South Africa's private healthcare sector is a complex and fragmented environment. There are 89 medical insurance companies, and a myriad of different managed care companies and administrators (24). At least 5 different GRP models are in use, each with its own criteria for cluster inclusion, pricing methodology, frequency of updates and reference prices. In the case of the studied GRP model, category-specific member and pharmacy communication is distributed prior to RP implementation; however it can be concluded that this communication is insufficient to invoke a substantial switch to generics. This is not surprising as it is impossible for a prescriber or dispenser to be familiar with every model. Consequently the impact of each GRP model is minimised. Systems that provide updated drug and reference price information and automatically apply reference pricing at the time of dispensing are available, but are mostly used by pharmacies and infrequently used by prescribers. Although generic substitution by dispensers

is mandatory in South Africa, pharmacy switching to lower priced generics is limited by drug availability. Pharmacies typically do not procure all available generics, and may not have the lowest priced products in stock. Dispensing incentives from certain suppliers may also impact which generic is dispensed.

Limitations

This study has several limitations that need to be considered. First, the sample population is small. Data is only available for a limited sector of the privately insured market, which insures approximately 8.76 million lives (24), and hence the results cannot be extrapolated to the entire private sector or to South Africa, a LMIC, as the majority of the population use public healthcare services (25). It is therefore limited in its representation of the impact of GRP in LMICs. Of the available data a substantial portion was not eligible due to variation in membership and/or the insurer's application of a host of managed care interventions which would act as confounders.

Second, the period of analysis is relatively short, particularly the pre-GRP implementation period. This may not allow complete assessment of the market dynamics. Third, only two GRP categories were eligible for review. Although there were similarities in the observations across these two categories, these results cannot be transferred to the GRP model as a whole.

Thirdly, DDDs have their limitations. DDDs are used for the measurement of drug utilisation and do not necessarily reflect the recommended or prescribed daily dose (PDDs). There may be significant differences between DDDs and PDDs (26).

Fourthly, this study does not take into account the potential prescribing switch which may occur, often as a result of originator market strategies. Physicians may prescribe an incremental innovative drug ('me-too drug') or a true patent-protected therapeutic alternative.

Finally, the study doesn't include an assessment of the impact of potential switching to non-referenced therapeutic alternatives. Any savings identified should take the expense on non-referenced alternatives into account.

Conclusion

The findings of this study are mostly consistent with literature published on the impact of GRP in high-income countries. It corroborates the overall price and expenditure decrease that is seen in most GRP implementation studies as patients switch to cheaper alternatives to the originator. However, the study also powerfully demonstrates that there are many other factors at work and that GRP by itself may be an inadequate strategy. In particular, the change in price, utilisation, expenditure and market share of Clopidogrel's AG, compared to lower priced generics raises some questions about the effectiveness of GRP as a pro-generic policy.

References

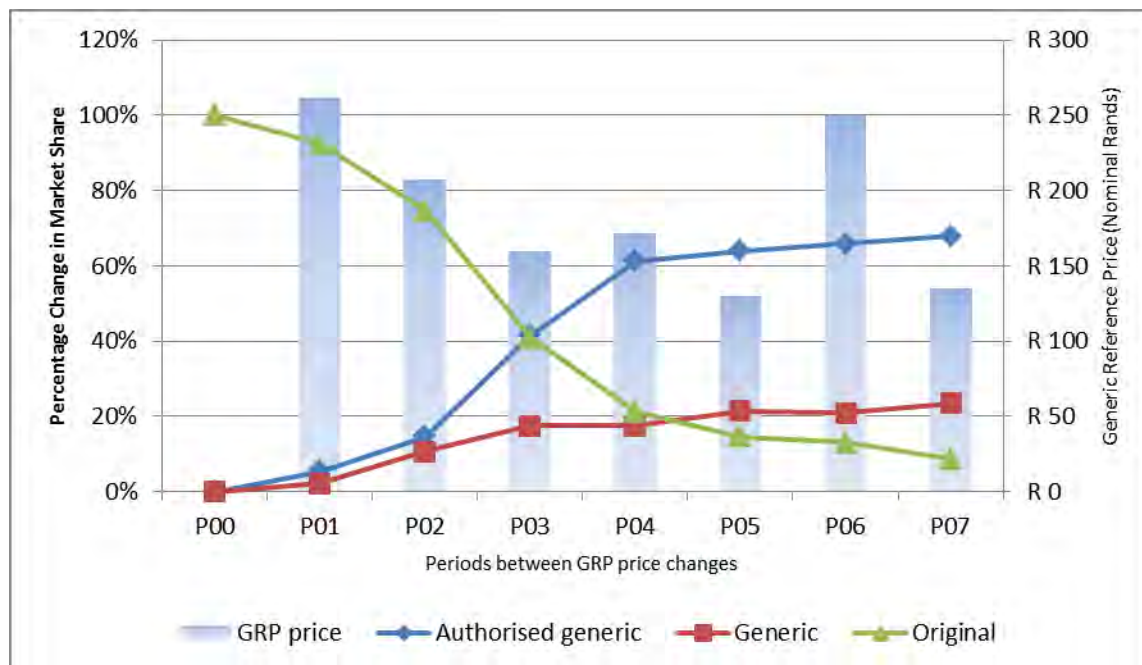
- (1) Organisation for Economic Co-operation and Development. *Pharmaceutical Pricing Policies in a Global Market*. 2008.
- (2) Intercontinental Marketing Services. Responsible use of Medicines. 2012; Available at: <http://www.imshealth.com/portal/site/imshealth/menuitem.762a961826aad98f53c753c71ad8c22a/?vgnextoid=faf9ee0a8e631410VgnVCM10000076192ca2RCRD&vgnextfmt=default>. Accessed September 4, 2014.
- (3) Hawkins L. WHO/HAI project on medicine prices and availability: Review series on pharmaceutical pricing policies and interventions: Working paper 4: Competition Policy. 2011.
- (4) Aaserud M, Austvoll-Dahlgren A, Kösters JP, Oxman AD, Ramsay C, Sturm H. Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies. The Cochrane Library 2006.
- (5) Puig-Junoy J, Moreno-Torres I. Do generic firms and the Spanish public purchaser respond to consumer price differences of generics under reference pricing? *Health Policy* 2010 12;98(2-3):186-194.
- (6) Magazzini L, Pammolli F, Riccaboni M. Dynamic Competition in Pharmaceuticals: Patent Expiry, Generic Penetration, and Industry Structure. *European Journal of Health Economics* 2004 06;5(2):175-182.
- (7) Moreno-Torres I, Puig-Junoy J, Borrell J. Generic Entry into the Regulated Spanish Pharmaceutical Market. *Review of Industrial Organization* 2009 06;34(4):373-388.
- (8) Kanavos P, Costa-Font J, Seeley E. Competition in off-patent drug markets: Issues, regulation and evidence. *Econ Policy* 2008;23(55):500-544.
- (9) Federal Trade Commission. Authorized generic drugs: short-term effects and long-term impact. Retrieved September 2011;10:2014.
- (10) López-Casasnovas G, Puig-Junoy J. Review of the literature on reference pricing. *Health Policy* 2000;54(2):87-123.
- (11) Crasto AM. New drug approvals. 2014; Available at: <http://newdrugapprovals.org/south-africa-mcc/>. Accessed August 14, 2014.
- (12) Department of Trade and Industry. Draft National Policy on Intellectual Property, 2013. 2013.
- (13) Faden L, Vialle-Valentin C, Ross-Degnan D, Wagner A. WHO/HAI Project on Medicine Prices and Availability. Review Series on Pharmaceutical Pricing Policies and Interventions . Working Paper 2: The Role of Health Insurance in the Cost-Effective Use of Medicines. . 2011.

- (14) Kaplan WA, Ritz LS, Vitello M, Wirtz VJ. Policies to promote use of generic medicines in low and middle income countries: A review of published literature, 2000-2010. *Health Policy* 2012 08;106(3):211-224.
- (15) Rothberg AD, Blignault J, Serfontein CB, Valodia B, Eekhout S, Pels LM. Experience of a medicines reference-pricing model. *S Afr Med J* 2004 03;94(3):183-188.
- (16) World Health Organisation. ATC/DDD Index. 2014; Available at: http://www.whocc.no/atc_ddd_index/. Accessed September 12, 2014.
- (17) Dylst P, Vulto A, Simoens S. The impact of reference-pricing systems in Europe: a literature review and case studies. *Expert Rev Pharmacoecon Outcomes Res* 2011 12;11(6):729-737.
- (18) Galizzi MM, Ghislandi S, Miraldo M. Effects of reference pricing in pharmaceutical markets: a review. *Pharmacoeconomics* 2011 01;29(1):17-33.
- (19) Simoens S, De Bruyn K, Bogaert M, Laekeman G. Pharmaceutical policy regarding generic drugs in Belgium. *Pharmacoeconomics* 2005;23(8):755-766.
- (20) Fiorio CV, Siciliani L. Co-payments and the demand for pharmaceuticals: evidence from Italy. *Econ Model* 2010;27(4):835-841.
- (21) von der Schulenburg F, Vondoros S, Kanavos P. The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors. *Health Econ Rev* 2011 11/21;1(1):18-18.
- (22) Puig-Junoy J. The impact of generic reference pricing interventions in the statin market. *Health Policy* 2007 11; 2013/4;84:14+.
- (23) Dunne S, Shannon B, Dunne C, Cullen W. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. *BMC Pharmacol Toxicol* 2013 01/05;14:1-1.
- (24) Council for Medical Schemes. Annual Report 2013-2014. 2014.
- (25) Council for Medical Schemes. Annual Report 2010-2011. 2011 2011.
- (26) Grimmsmann T, Himmel W. Discrepancies between prescribed and defined daily doses: a matter of patients or drug classes? *Eur J Clin Pharmacol* 2011; 67(8): 847–854.

Online Appendix

Figure A: Change in the Clopidogrel market share in relation to GRP changes

(a) Change in market share by cost



(b) Change in market share by volume

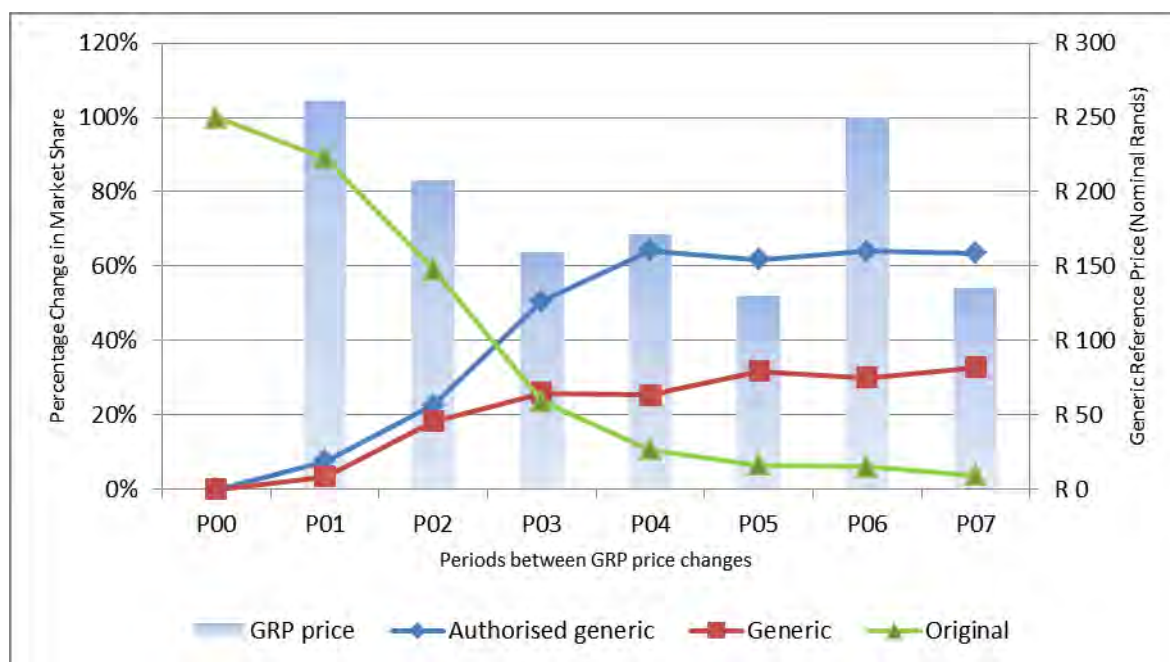


Figure B: Change in Desloratadine market share in relation to GRP changes

(a) Market share by value



(b) Change in market share by volume

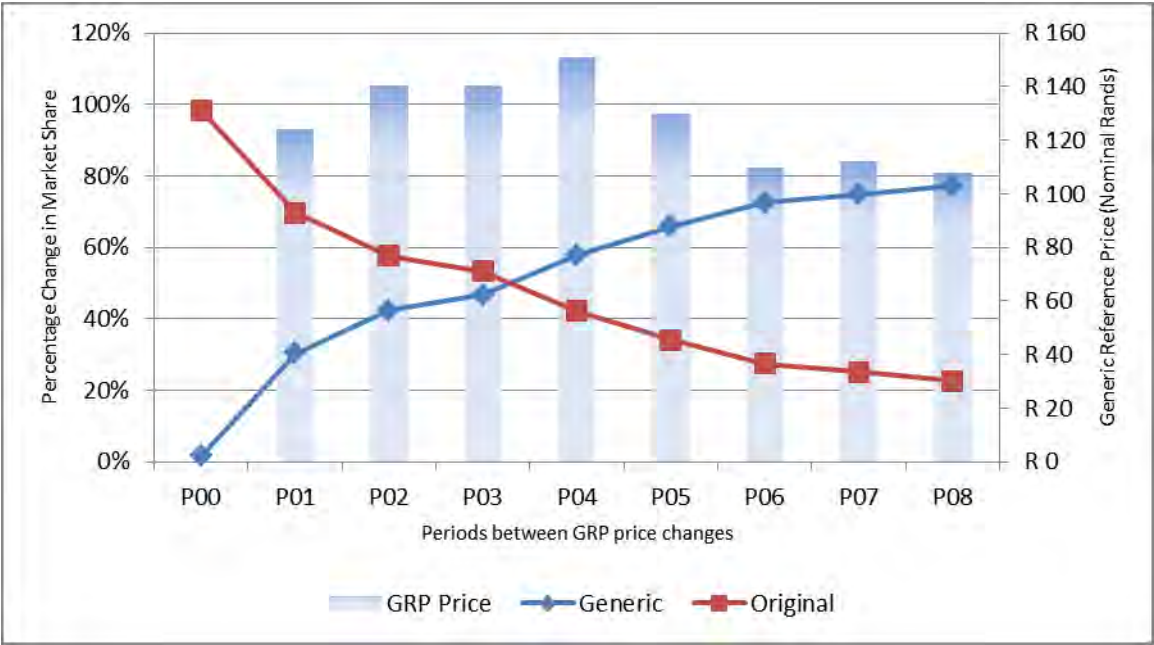


Table A: Identified GRP categories and related products

GRP Category	GRP Effective date	Study period (includes 4 months pre-GRP implementation)	No. of products in cluster	Drug Classification	Defined daily dose
Clopidogrel 75mg	13 January 2009	13 Sept 2008 – 3 May 2013	7	Platelet aggregation inhibitor ATC: B01AC04 (Chronic use)	75mg (1 tablet)
Desloratadine 5mg	28 April 2008	1 Jan 2008 – 3 May 2013	5	Antihistamine ATC: R06AX27 (Acute and chronic)	5mg (1 tablet)

Table B: ‘Period’ allocation and time intervals per generic reference price (GRP) category

	Clopidogrel bisulphate 75 mg			Desloratadine 5 mg		
Period number	Start date	End date	No. of days	Start date	End date	No. of days
P00	09/13/2008	01/12/2009	122	01/01/2008	04/27/2008	118
P01	01/13/2009	02/14/2009	33	04/28/2008	04/05/2009	343
P02	02/15/2009	06/30/2009	136	04/06/2009	09/30/2009	178
P03	07/01/2009	05/13/2010	317	10/01/2009	05/13/2010	225
P04	05/14/2010	12/31/2010	232	05/14/2010	09/30/2010	140
P05	01/01/2011	02/05/2012	401	10/01/2010	10/31/2011	396
P06	02/06/2012	08/31/2012	208	11/01/2011	03/05/2012	126
P07	09/01/2012	03/05/2013	186	03/06/2012	10/31/2012	240
P08	N/A	N/A	N/A	11/01/2012	03/05/2013	125
Total			1635			1891

Part D: Policy Brief



HEALTH
ECONOMICS
UNIT



*School of Public Health &
Family Medicine*

University of Cape Town

About the study:

The research presented in this paper was conducted by Jenni Noble-Luckhoff to fulfil the requirements for a MPH (health economics) from the University of Cape Town.

Acknowledgements:

Professor Di McIntyre who supervised the study.

MediKredit Integrated Healthcare Solutions for enabling access to data and Yvette van der Westhuizen for her assistance with data extraction and collation.

Lourens Wepener and Medscheme Holdings Pty (Ltd) for assistance in data management and analysis.

What more can be done to promote the use of generic medicines?

Key Points

- Increased use of generic drugs can reduce expenditure on medicines and decrease the burden of out-of-pocket payments.
- Generic reference pricing is a pro-generic policy that effectively reduces the overall expenditure and price of referenced drugs and increases generic utilisation.
- 'Authorised generics' are launched by originator companies to reduce the impact of generic entry to market. They effectively reduce the impact of generic reference pricing by rapidly gaining market share.
- Prescribing by the international non-proprietary name (INN), or generic name, may effectively counter these marketing strategies.

INTRODUCTION

Healthcare financing in the context of the global emphasis on universal health coverage aims to prefund healthcare expenditure and protect against financial risk. In South Africa approximately 8.8 million people are covered by medical schemes (voluntary health insurance). The objective

of healthcare insurance is to enable access to healthcare services and reduce out-of-pocket (OOP) payments. However, South African medical scheme members fund more than 60% of the country's total OOP

payments⁶. A recent report from the Council for Medical Schemes indicates that a quarter of this sector's OOP expenditure is attributable to medicine⁷.

Increased use of generic medication reduces these OOP payments as well as reduces overall healthcare expenditure. Inter-continental Marketing Services (IMS) has indicated that the global use of low-cost generics could generate savings of 19 to 40 billion US dollars. However manufacturers of originator drugs try to protect their market share by limiting the entry and penetration of generics through a variety of marketing tactics. One such tactic is the launch of an 'authorised generic' or

'clone' (see Box 1 for a description).

Many pro-generic strategies are available. These include measures that address both supply and demand. There is however no consensus as to which combination of pro-generic strategies is most effective.

Generic reference pricing (GRP) is a pro-generic system that largely impacts supply-side factors, but also has an impact on demand through the application of OOP payments (see Box 2). The impact of GRP in South Africa is not well researched. For this reason a study was conducted on a GRP system operational in South Africa's privately insured sector.

Box 1: What is an 'authorised generic' or 'clone'?

This is a drug that is an exact copy of the originator

- It is approved as a brand-name drug under patent protection but marketed as a generic
- It is manufactured either by the originator company or in accordance with the originator company's specifications

Box 2: What is generic reference pricing (GRP)?

GRP is a system of controlled reimbursement:

- A maximum reimbursement price is set for a group of chemically equivalent, interchangeable medicines
- The patient pays the difference between the reference price and the price of the prescribed or dispensed drug, if the dispensed drug price is higher

METHODS

The objective of this study was to determine the impact of one of the GRP systems used in South African medical schemes. A time series intervention study was conducted on up to 5 years of unidentifiable patient level claims records for two identified categories of GRP, Clopidogrel, an anti-thrombotic drug and Desloratadine, an antihistamine.

⁶ McIntyre, D., Doherty, J. & Ataguba, J. 2012. Health care financing and

expenditure. In: VAN RENSBURG, H. (ed.) *Health and health care in South Africa*.

⁷ Council for Medical Schemes, 2015. Out of Pocket Payments by Medical Scheme Members. 2 Feb 2015

The total study was divided into multiple ‘periods of analysis’. These are time intervals before GRP implementation and between subsequent GRP price changes. These time intervals vary substantially in duration because the GRP price change dates are not consistent.

The impact of GRP on drug price, expenditure, market share and OOP payments was then reviewed. The changes in these parameters were tracked from pre-implementation of GRP to post-implementation as well as across subsequent price changes of GRP. In each case the impact on the originator drug, the

generics and where applicable, the authorised generic was determined. Only the Clopidogrel reference category studied had an authorised generic.

KEY FINDINGS

Results that were common to both GRP categories were firstly that the overall expenditure on drugs in each category decreased, despite the volume of drugs dispensed increasing over the study period. Secondly it was established that GRP had no impact on the price of the originator product in both categories. The originator products continued to increase annually by the permitted

single exit price (SEP) increase.

For both categories the originator rapidly lost market share, however the extent of the decline differed. For Clopidogrel the originator’s market share (by volume) declined to almost 4% while Desloratadine’s originator declined to 22% (see Figures 1 and 2).

Clopidogrel’s authorised generic initially reduced in price to match the reference price, but then increased in line with the permitted single exit price increase, irrespective of any changes in the reference price. Nonetheless the authorised generic rapidly gained

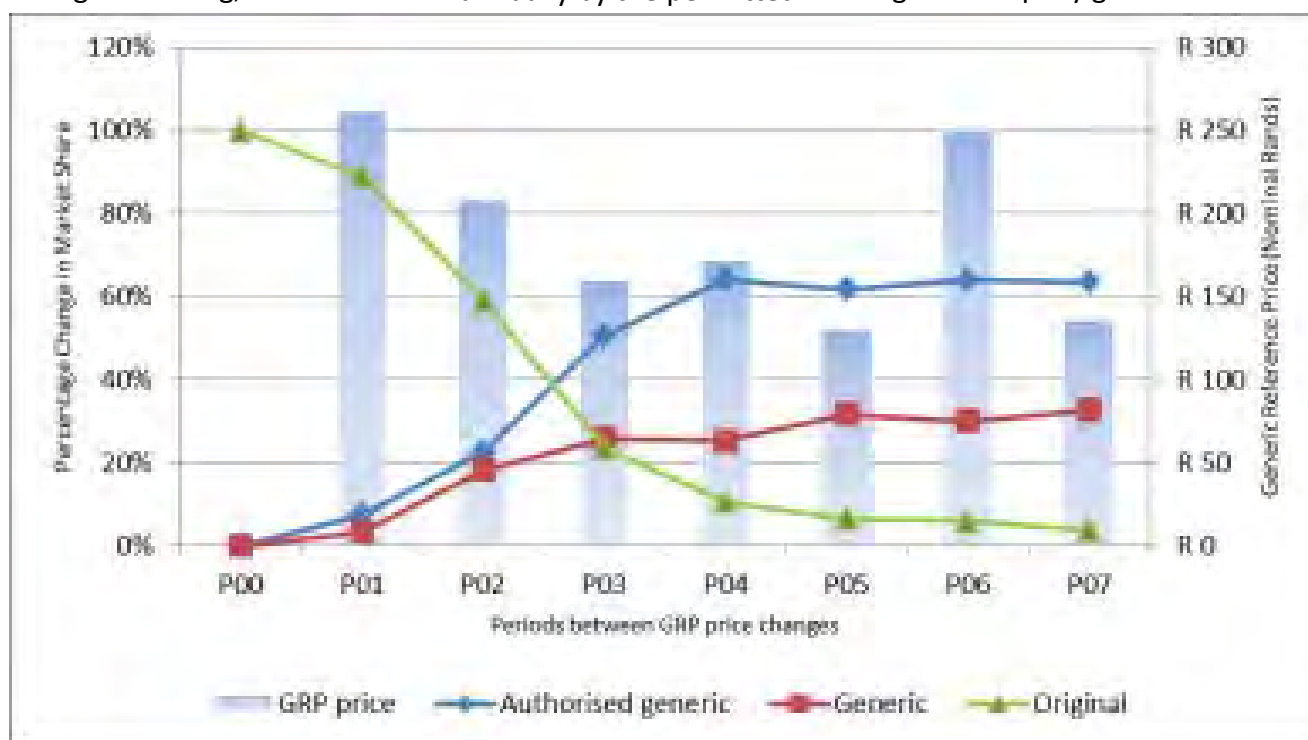


Figure 1: Change in **Clopidogrel’s** Market Share (by volume) in relation to reference price changes

market share, capturing and maintaining almost two thirds of the market despite an increasing quantum of co-payment applying. Clopidogrel's generic drugs on the other hand only gained one third of the market despite their prices being lower than the authorised generic prices and co-payments being minimal.

There was no notable change in Clopidogrel's overall out-of-pocket expenditure. The percentage of drugs subject to an OOP payment only decreased marginally.

Results for the Desloratadine reference category which did not have an authorised generic revealed a difference in the impact on market share movement. For Desloratadine the generic market share increased continuously, capturing 80% of the market by the end of the study (see figure 2). As with Clopidogrel there was little variation in total drug expenditure paid out-of-pocket, but unlike Clopidogrel there was a dramatic decrease in the percentage of drugs

dispensed that had a co-payment

WHAT DO THESE FINDINGS MEAN?

The intention of generic reference pricing is to reduce the overall expenditure on medicines by encouraging patients to switch to using generic medicine, and in so doing minimising OOP payments while simultaneously encouraging product price cuts. This empirical study supports the findings of international studies that indicate that GRP reduces overall expenditure by stimulating price competition. However this study also highlights the effectiveness of an originator manufacturer's marketing strategy in launching an authorised generic.

Figure 2: Change in **Desloratadine's** Market Share (by volume) in relation to reference price changes

The strategy of an authorised generic plays on doctors' and pharmacists' brand loyalty as well as their quality perceptions of generics. The quality of the authorised generic is frequently perceived to be higher than that of other generics.

This study suggests the issue of asymmetry in the relationship between a provider and patient, which may impact a patient's price sensitivity. In this analysis patients appear to be willing-to-pay increasing co-payments, despite the availability of generic alternatives with no or minimal co-payments. The study reinforces the importance of addressing

demand-side issues when implementing pro-generic policies.

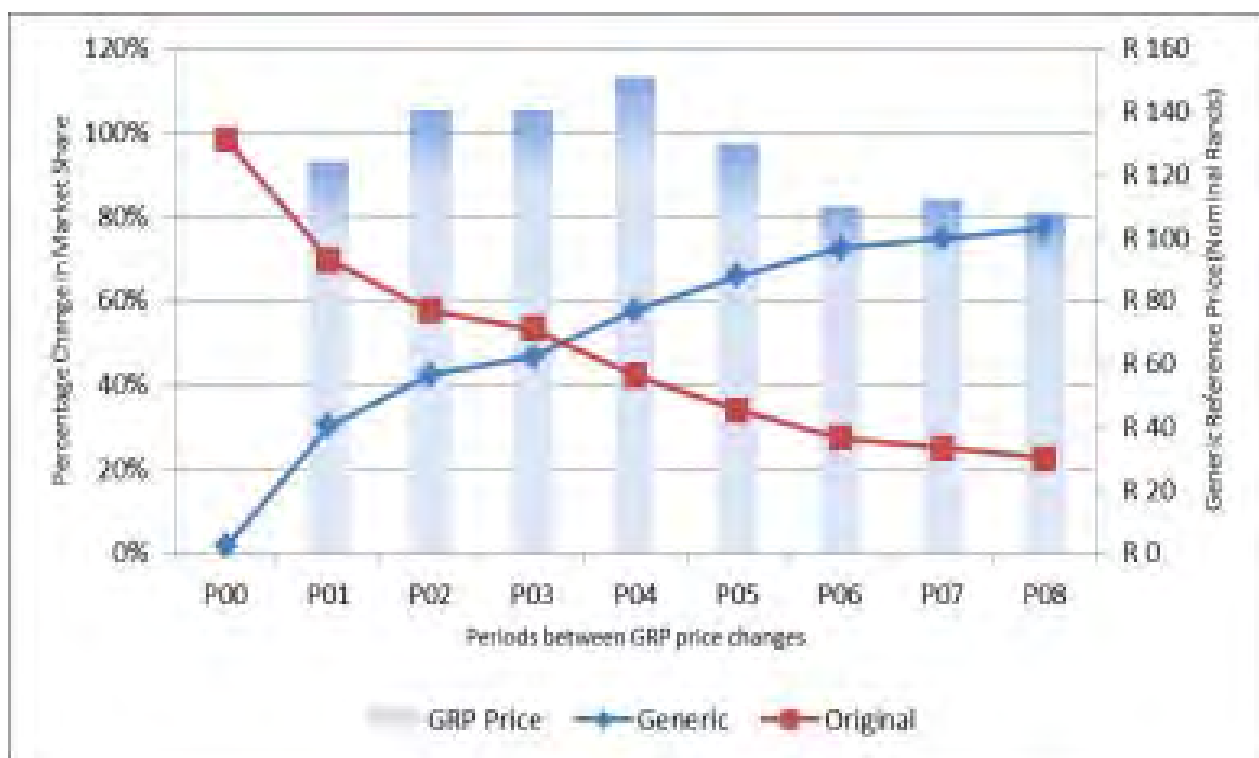
STUDY LIMITATIONS

Unfortunately the sample size of patients and number of GRP categories analysed was limited and was only representative of one of several GRP systems in South Africa's private sector. Nevertheless the fact that several international empirical studies have shown similar results supports the findings and proposed policy indications.

POLICY IMPLICATIONS

As the impact of originator manufacturers' marketing strategies to hinder generic entry and penetration are seen to be highly effective, a major battle needs to be waged to counter these strategies. Medicines policy needs to focus on demand side measures.

One policy that has been effective in promoting the utilisation of generic medicines is mandatory prescribing by the international non-proprietary name (INN), or generic name. Prescribing by INN is attributed as a key driver in achieving 83% generic utilisation rates in the United Kingdom in 2009/2010⁸, one of the



highest rates in the world. INN prescribing is listed as a recommended policy to reduce drug costs and expenditure in South Africa's National Drug Policy of 1996. This policy, in combination with the current regulations enforcing mandatory generic substitution, as well as education on generic prescribing and generic acceptance should align prescribers and dispensers to improve generic utilisation and reduce OOP payments.

This brief therefore makes the following recommendations:

- Enforce mandatory prescribing by INN in private and public sectors;
- Emphasise education on generic prescribing in medical training;
- Active promotion of generic acceptance by prescribers and dispensers of medicine, patients and the community as a whole.

Part E:

Appendices

Appendix A: List of Data Fields required per GRP Category

MMAP code
Active ingredient name and strength
Dosage form
Category effective date
Category termination date (if currently applicable)
Temporary withdrawals? Y/N
If Y, effective & termination date of withdrawal
Price history (from 1 January 2007 – 31 July 2013):
Effective date, price and associated pack size
Effective date, price and associated pack size
Effective date, price and associated pack size etc.
Defined Daily Dose (DDD)

Appendix B: List of Data Fields Required for Claims from MediKredit

Data fields to be requested for each claim line should include the following:

Date of claim
Product code (NAPPI code)
Product name
Product strength
Product dosage form
Product quantity dispensed
Generic ingredient, dosage form & strength description
Generic/original flag indicator
Gross cost (including VAT, excluding dispensing fee)
Nett cost (including VAT, excluding dispensing fee)
Product SEP (including VAT)
MMAP cost per unit (excluding dispensing fee)
Calculated MMAP (based on dispensed quantity)
MMAP Out-of-Pocket Payment

Appendix C: List of Data Fields required for All Products mapping to Sample MMAP Categories

Product Code (NAPPI code)
Product Name
Product dosage form
Generic ingredient, strength & form description
Launch date
Termination date
Generic/Original indicator
SEP (including VAT) and associated pack size (repeat for all SEP updates from 1 January 2007 to 31 July 2013)
SEP Effective date (repeat for all SEP updates from 1 January 2007 to 31 July 2013)
Manufacturer

Appendix D: Ethics Approval Letter



UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Ms S Ariefdien - Tel: [021]4066492 • Fax: [021]4066411
email: sumayah.ariefdien@uct.ac.za

14 November 2011

HREC REF: 535/2011

Dr J Noble-Luckhoff,
Public Health and Family Medicine
Falmouth Building

CC: Prof D McIntyre
Health Economics Unit
Public Health & Family Medicine
Falmouth Building

Dear Dr Noble-Luckhoff,

PROJECT TITLE: A CRITICAL ANALYSIS OF THE IMPACT OF GENERIC MEDICINE REFERENCE PRICING IN THE SOUTH AFRICAN PRIVATE HEALTHCARE INSURANCE INDUSTRY

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Approval is granted until 15 November 2012

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file (FHS010).

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN

CHAIRPERSON, FHS HUMAN RESEARCH ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethical Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 312.60, 312.61 and 312.62.

Appendix E: Journal instruction to authors



HEALTH POLICY

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

ISSN: 0168-8510

• Description	p.1
• Audience	p.2
• Impact Factor	p.2
• Abstracting and Indexing	p.2
• Editorial Board	p.2
• Guide for Authors	p.4

DESCRIPTION

Health Policy is intended to be a vehicle for the exploration and discussion of **health policy** and **health system** issues and is aimed in particular at enhancing communication between health policy and system researchers, legislators, decision-makers and professionals concerned with developing, implementing, and analysing health policy, health systems and health care reforms, primarily in high-income countries outside the U.S.A.

Health care policies and reforms are made at an ever-increasing pace in countries around the world - and policy-makers are increasingly looking to other countries for solutions to their own problems. *Health Policy* is committed to support this international dialogue to ensure that policies are not just copied but used and adapted based on the specific problems and objectives as well as the respective context. The journal encourages the **submission** of short, full-length, comparative and review articles (as well as groups of articles in "special sections") which address:

1. What is happening in terms of policies, reforms, regulation etc. of health systems;
2. Where the ideas are coming from, i.e. whether they are "imported" from another country or developed within the country, and how innovative they are they in comparison to other countries;
3. Why it is happening, e.g. as a consequence of a change in government, popular dissatisfaction or (perceived) unsustainable cost increases, and what are the objectives;
4. The actors involved (both governmental as well as non-governmental), incl. their roles, their opinions and their strength in the decision and implementation process;
5. Intended and, especially, unintended effects of these policies or reforms on the health system in terms of access, appropriateness, costs, effectiveness, quality, patient experience and equity etc.; and
6. Their final consequences in terms of health outcomes, financial protection and responsiveness to the population's legitimate expectations, i.e. a performance assessment of reforms and health systems.

To achieve the journal's objectives, authors are encouraged to write in a non-technical style, which is understandable to health policy practitioners and specialists from other disciplines and in other countries.

Please submit your article via <http://ees.elsevier.com/heap>.

Health Policy is ranked 33rd out of 70 journals in the Health Policy & Services category in the 2013 Journal Citation Reports, published by Thomson Reuters, and has an Impact Factor of 1.725.

Electronic usage An increasing number of readers access the journal online via ScienceDirect, one of the world's most advanced web delivery systems for scientific, technical and medical information, and through the journal's web site, healthpolicyjrn.com

2013 Usage:

44,007 average monthly article downloads on [ScienceDirect](#)

21,813 average monthly pageviews on [healthpolicyjml.com](#)

AUDIENCE

Legislators; Health Services Researchers; Healthcare Providers and Planners; Policy Analysts; Healthcare Insurers; Health Related Industry; Healthcare Foundations

IMPACT FACTOR

2013: 1.725 © Thomson Reuters Journal Citation Reports 2014

ABSTRACTING AND INDEXING

CINAHL
Current Contents/Health Services Administration
Current Contents/Social & Behavioral Sciences
MEDLINE®
EMBASE
HealthSTAR
Hospital and Health Administration Index
Public Affairs Information Service Bulletin
Reference Update
Social Sciences Citation Index
Sociological Abstracts
CSA Database
Scopus
PsychINFO

EDITORIAL BOARD

Editor-in-Chief

Reinhard Busse, Department of Health Care Management, Berlin University of Technology, Berlin, Germany

Editorial Office (Managing Editors)

Irene Papanicolas, Willem Quentin, Leonie Sundmacher, Julia Röttger

Associate Editors

Giovanni Fattore, Milan, Italy
Jane Hall, Sydney, New South Wales, Australia
Naoki Ikegami, Tokyo, Japan
Zeynep Or, Paris, France
Peter Smith, London, UK
Jason Sutherland, Vancouver, British Columbia, Canada
Wynand P.M.M. Van De Ven, Rotterdam, Netherlands
Claus Wendt, Siegen, Germany

Editorial Board

Toni Ashton, Auckland, New Zealand
Luca Crivelli, Lugano, Switzerland
Karen Davis, New York, New York, USA
Sabina De Geest, Basel, Switzerland
Anna Dixon, London, England, UK
Michael Drummond, York, UK
Josep Figueras, Brussels, Belgium
Julio Frenk, Mexico City, Mexico

Livio Garattini, Ranica, Italy
Unto Häkkinen, Helsinki, Italy
Maria Hofmarcher, Vienna, Austria
Panos Kanavos, London, England, UK
Hans Maarse, Maastricht, Netherlands
Jose M Martin-Moreno, Valencia, Spain
Alan Maynard, York, UK
Ellen Nolte, Cambridge, England, UK
John Ovreteit, Stockholm, Sweden
Uwe Reinhardt, Princeton, New Jersey, USA
John-Arne Røttingen, Oslo, Norway
Erik Schokkaert, Leuven, Belgium
Amir Shmueli, Jerusalem, Israel

GUIDE FOR AUTHORS

Health Policy is intended to be a vehicle for the exploration and discussion of health policy issues and is aimed in particular at enhancing communication between health policy researchers, legislators, decision-makers and professionals concerned with developing, implementing, and analysing health policy in high-income countries primarily outside the US.

Health care policies and reforms are made at an ever-increasing pace in countries around the world - and policy-makers are increasingly looking to other countries for solutions to their own problems. Health Policy is committed to support this international dialogue to ensure that policies are not just copied but used and adapted based on the specific problems and objectives as well as the respective context. Articles in Health Policy should thus describe and analyze

1. what is happening in terms of policies, reforms, regulation etc. of health systems;
2. where are the ideas coming from, i.e. are they "imported" from another country or are they developed within the country - and how innovative are they in comparison to what is happening in other countries;
3. why is it happening, e.g. as a consequence of a change in government, popular dissatisfaction, (perceived) unsustainable cost increases or an international requirement, and what are the objectives;
4. the actors involved (both governmental as well as non-governmental including scientists, the media and the public), what are their roles, their opinions and their strength in the decision and implementation process;
5. intended and, especially, unintended effects of these policies or reforms on the health system in terms of access, appropriateness, costs, effectiveness, quality, patient experience and equity etc.; and last but not least
6. their final consequences in terms of health outcomes, financial protection and responsiveness to the population's legitimate expectations, i.e. a performance assessment of reforms and health systems.

To achieve the journal's objectives, authors are encouraged to write in a non-technical style, which is understandable to health policy practitioners and specialists from other disciplines. The use of overly technical tables (e.g. full of regression models) or equations is discouraged or should be placed in the supplementary material.

Types of Contribution

Health Policy will be accepting submissions in three different formats:

- (1) "Health reform monitor" of around 2,000 words (excluding abstract and references), concentrating on proposed, discussed, just passed and/ or implemented reforms in one of the Health Systems and Policy Monitor member. These do not have to present empirical data but analyze actors and processes.
- (2) "Full-length articles" of around 4,000 words (and not more than 4,500 words), mainly empirical, analyzing the impact of health systems, reforms and policies - both in terms of intended and unintended effects. In addition, more theoretical, conceptual or methodological papers can be submitted.
- (3) "Reviews/comparative analyses" of around 6,000 words (and not more than 7,000 words) can either be
 - (a) systematic reviews of health policy measures
 - (b) or examine certain aspects of health systems or health reforms in a systematic, comparative manner across a number of countries. Such papers may additionally include experience from countries outside the primary focus of the journal.

In all cases, Authors should provide sufficient background and context and discuss their findings in an international context, to ensure that their manuscript can be appreciated by an international readership.

Besides these three main types of submissions, Health Policy is interested in publishing debate among the readers in the form of letters and repliques as well as commissioned editorials.

For all types of submissions, the material should not have been previously published in peer-review journals elsewhere. Publication as an abstract, academic thesis or discussion paper is permissible but needs to be stated in the cover letter to the editor upon submission.

Size and Layout

Manuscripts should be written in English. They should be clear, concise and logical, and follow the suggested word length (see above) as well as the number of tables and figures (see below).

Manuscripts should be structured as follows (if appropriate; e.g. Health Reform Monitor articles may differ): • Cover letter • Title Page (incl. Acknowledgements, e.g. to sponsors, and Conflict of Interest statement) • Abstract • Introduction • Materials and methods • Results • Discussion • Conclusions (especially for policy-makers and international audience) • Appendices (will be included as online supplementary material if the manuscript is accepted).

There should be no footnotes or endnotes in the manuscript.

Manuscripts that do not comply with the above mentioned manuscript guidelines will be considered as non-admissible. All submissions will be checked for plagiarism. The handling editor will be informed about any incorrectly cited text passages/ findings of plagiarism.

Figures, tables and equations

Figures and tables are encouraged but should not be too technical. Technical tables and especially equations or other formulae should be avoided. Except in exceptional circumstances, the admissible number of figures and tables together is 2 for Health Reform Monitor articles, 4 for full-length articles and 6 for reviews and comparative articles. Additional figures and tables may be supplied as supplementary material. Figures and tables should still be legible when reduced in size for printing (for more details see below).

BEFORE YOU BEGIN

Ethics in publishing

For information on Ethics in publishing and Ethical guidelines for journal publication see <http://www.elsevier.com/publishingethics> and <http://www.elsevier.com/journal-authors/ethics>.

Conflict of interest

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. See also <http://www.elsevier.com/conflictsofinterest>. Further information and an example of a Conflict of Interest form can be found at: http://help.elsevier.com/app/answers/detail/a_id/286/p/7923.

Submission declaration

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or academic thesis or discussion paper; see <http://www.elsevier.com/postingpolicy>), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

Changes to authorship

This policy concerns the addition, deletion, or rearrangement of author names in the authorship of accepted manuscripts:

Before the accepted manuscript is published in an online issue: Requests to add or remove an author, or to rearrange the author names, must be sent to the Journal Manager from the corresponding author of the accepted manuscript and must include: (a) the reason the name should be added or removed,

or the author names rearranged and (b) written confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed. Requests that are not sent by the corresponding author will be forwarded by the Journal Manager to the corresponding author, who must follow the procedure as described above. Note that: (1) Journal Managers will inform the Journal Editors of any such requests and (2) publication of the accepted manuscript in an online issue is suspended until authorship has been agreed.

After the accepted manuscript is published in an online issue: Any requests to add, delete, or rearrange author names in an article published in an online issue will follow the same policies as noted above and result in a corrigendum.

Copyright

This journal offers authors a choice in publishing their research: Open access and Subscription.

For subscription articles

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (for more information on this and copyright, see <http://www.elsevier.com/copyright>). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations (please consult <http://www.elsevier.com/permissions>). If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases: please consult <http://www.elsevier.com/permissions>.

For open access articles

Upon acceptance of an article, authors will be asked to complete an 'Exclusive License Agreement' (for more information see <http://www.elsevier.com/OAauthoragreement>). Permitted reuse of open access articles is determined by the author's choice of user license (see <http://www.elsevier.com/openaccesslicenses>).

Retained author rights

As an author you (or your employer or institution) retain certain rights. For more information on author rights for:

Subscription articles please see <http://www.elsevier.com/journal-authors/author-rights-and-responsibilities>.

Open access articles please see <http://www.elsevier.com/OAauthoragreement>.

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.

Funding body agreements and policies

Elsevier has established agreements and developed policies to allow authors whose articles appear in journals published by Elsevier, to comply with potential manuscript archiving requirements as specified as conditions of their grant awards. To learn more about existing agreements and policies please visit <http://www.elsevier.com/fundingbodies>.

Open access

This journal offers authors a choice in publishing their research:

Open access

- Articles are freely available to both subscribers and the wider public with permitted reuse
- An open access publication fee is payable by authors or their research funder

Subscription

- Articles are made available to subscribers as well as developing countries and patient groups through our access programs (<http://www.elsevier.com/access>)

- No open access publication fee

All articles published open access will be immediately and permanently free for everyone to read and download. Permitted reuse is defined by your choice of one of the following Creative Commons user licenses:

Creative Commons Attribution-NonCommercial-ShareAlike (CC BY-NC-SA): for non-commercial purposes, lets others distribute and copy the article, to create extracts, abstracts and other revised versions, adaptations or derivative works of or from an article (such as a translation), to include in a collective work (such as an anthology), to text and data mine the article, as long as they credit the author(s), do not represent the author as endorsing their adaptation of the article, do not modify the article in such a way as to damage the author's honor or reputation, and license their new adaptations or creations under identical terms (CC BY-NC-SA).

Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND): for non-commercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.

Elsevier has established agreements with funding bodies, <http://www.elsevier.com/fundingbodies>. This ensures authors can comply with funding body open access requirements, including specific user licenses, such as CC BY. Some authors may also be reimbursed for associated publication fees. If you need to comply with your funding body policy, you can apply for the CC BY license after your manuscript is accepted for publication.

To provide open access, this journal has a publication fee which needs to be met by the authors or their research funders for each article published open access.

Your publication choice will have no effect on the peer review process or acceptance of submitted articles.

The open access publication fee for this journal is **\$2,500**, excluding taxes. Learn more about Elsevier's pricing policy: <http://www.elsevier.com/openaccesspricing>.

Language (usage and editing services)

Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel or who are informed in this regard by the editors that their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop (<http://webshop.elsevier.com/languageediting/>) or visit our customer support site (<http://support.elsevier.com>) for more information.

Submission

Submission to this journal proceeds totally online and you will be guided stepwise through the creation and uploading of your files. The system automatically converts source files to a single PDF file of the article, which is used in the peer-review process. Please note that even though manuscript source files are converted to PDF files at submission for the review process, these source files are needed for further processing after acceptance. All correspondence, including notification of the Editor's decision and requests for revision, takes place by e-mail removing the need for a paper trail.

Submit your article

Please submit your article via <http://ees.elsevier.com/heap>.

PREPARATION

Double-blind review

This journal uses double-blind review, which means that both the reviewer and author name(s) are not allowed to be revealed to one another for a manuscript under review. The identities of the authors are concealed from the reviewers, and vice versa. For more information please refer to <http://www.elsevier.com/reviewers/peer-review>. To facilitate this, please include the following separately:

Title page (with author details): This should include the title, authors' names and affiliations, and a complete address for the corresponding author including telephone and e-mail address. Acknowledgements and the Conflict of Interest statement also need to be included here.

Blinded manuscript (no author details): The main body of the paper (including the references, figures, tables should not include any identifying information, such as the authors' names or affiliations.

Essential title page information

- **Title.** Be concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae.
- **Author names and affiliations.** Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
- **Corresponding author.** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. **Ensure that phone numbers (with country and area code) are provided in addition to the e-mail address and the complete postal address. Contact details must be kept up to date by the corresponding author.**
- **Present/permanent address.** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.
- **Acknowledgements**
- **Conflict of Interest statement**

Cover letter

The cover letter is intended for the editors to assist them in their assessment whether the article fits the scope of the journal. Therefore, authors should repeat the information given in the abstract and/or highlights but briefly explain why they see *Health Policy* as the appropriate journal; this is even more important if the fit with the journal's scope and objectives is not immediately obvious. The authors should also point to important considerations that the editor should know when assigning the manuscript or sending it for review. For example, authors who have discussed their manuscript with an editor prior to submission should indicate this in the cover letter. Previous publication as an abstract, academic thesis or discussion paper should also be stated, and the appropriate sources given.

Abstract

An abstract of 200 words (and not more than 220) must be included in the submitted manuscript. As the abstract is often viewed separately from the article, it must be able to stand alone. It should state briefly and clearly the purpose and setting, the principal findings and major conclusions, and the paper's contribution to knowledge. If applicable, the country/countries/locations should be clearly stated, as should the methods and nature of the sample, the dates, and a summary of the findings/conclusion. Please note that excessive statistical details should be avoided, abbreviations/acronyms used only if essential or firmly established, and the abstract should not contain references to other published work.

Graphical abstract

Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. See <http://www.elsevier.com/graphicalabstracts> for examples.

Authors can make use of Elsevier's Illustration and Enhancement service to ensure the best presentation of their images and in accordance with all technical requirements: [Illustration Service](#).

Highlights

Highlights are mandatory for this journal. They consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 12 words per bullet point, please write in complete sentences, avoid using abbreviations). See <http://www.elsevier.com/highlights> for examples.

Classification and keywords

Authors are asked to classify their submission using the provided classification system. They are also asked to include 3 to 6 keywords, preferably from the Medical Subject Headings from *Index Medicus*.

Artwork

Electronic Artwork (Figures)

General points

- Make sure you use uniform lettering and sizing of your original artwork.
- Embed the used fonts if the application provides that option.
- Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Provide captions to illustrations separately.
- Size the illustrations close to the desired dimensions of the printed version.
- Submit each illustration as a separate file.

A detailed guide on electronic artwork is available on our website:

<http://www.elsevier.com/artworkinstructions>

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.

Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings, embed all used fonts.

TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.

TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.

TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.

Please do not:

- Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
- Supply files that are too low in resolution;
- Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color on the Web (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article.** Please indicate your preference for color: in print or on the Web only. For further information on the preparation of electronic artwork, please see <http://www.elsevier.com/artworkinstructions>.

Please note: Because of technical complications that can arise by converting color figures to 'gray scale' (for the printed version should you not opt for color in print) please submit in addition usable black and white versions of all the color illustrations.

Illustration services

Elsevier's WebShop (<http://webshop.elsevier.com/illustrationservices>) offers Illustration Services to authors preparing to submit a manuscript but concerned about the quality of the images accompanying their article. Elsevier's expert illustrators can produce scientific, technical and medical-style images, as well as a full range of charts, tables and graphs. Image 'polishing' is also available, where our illustrators take your image(s) and improve them to a professional standard. Please visit the website to find out more.

Figure captions

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article.

Throughout the manuscript text, Authors must indicate where approximately the figures and tables should be included.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is encouraged.

Web references

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

References in a special issue

Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference formatting

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal is VANCOUVER NUMBERED and will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct. If you do wish to format the references yourself they should be arranged according to the following examples:

Reference style

Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.

List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.

Examples:

Reference to a journal publication:

[1] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *J Sci Commun* 2010;163:51–9.

Reference to a book:

[2] Saltman RB, Busse R, Figueras J, editors. *Social health insurance systems in western Europe*. Berkshire: Open University Press; 2004.

Reference to a chapter in an edited book:

[3] McGlynn E. Measuring clinical quality and appropriateness. In: Smith P, Mossialos E, Papanicolas I, Leatherman S, editors. *Performance measurement for health system improvement experiences, challenges and prospects*. Cambridge: Cambridge University Press; 2009, p. 87–113. Reference to an electronic source:

[4] International Monetary Fund. Greece: stand-by arrangement - Review under the emergency financing mechanism. Country report no.10/217. Washington, DC: IMF; 2010. Available at: <http://www.imf.org/external/pubs/ft/scr/2010/cr10217.pdf> [accessed 10.08.13].

Note shortened form for last page number: e.g., 51–9, and that for more than 6 authors the first 6 should be listed followed by 'et al.' For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;277:927–34) (see also http://www.nlm.nih.gov/bsd/uniform_requirements.html).

Video data

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the files in one of our recommended file formats with a preferred maximum size of 50 MB. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect: <http://www.sciencedirect.com>. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages at <http://www.elsevier.com/artworkinstructions>. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

AudioSlides

The journal encourages authors to create an AudioSlides presentation with their published article. AudioSlides are brief, webinar-style presentations that are shown next to the online article on ScienceDirect. This gives authors the opportunity to summarize their research in their own words and to help readers understand what the paper is about. More information and examples are available at <http://www.elsevier.com/audioslides>. Authors of this journal will automatically receive an invitation e-mail to create an AudioSlides presentation after acceptance of their paper.

Supplementary material

Elsevier accepts electronic supplementary material to support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, high-resolution images, background datasets, sound clips and more. Supplementary files supplied will be published online alongside the electronic version of your article in Elsevier Web products, including ScienceDirect: <http://www.sciencedirect.com>. In order to ensure that your submitted material is directly usable, please provide the data in one of our recommended file formats. Authors should submit the material in electronic format together with the article and supply a concise and descriptive caption for each file. For more detailed instructions please visit our artwork instruction pages at <http://www.elsevier.com/artworkinstructions>.

Submission checklist

The following list will be useful during the final checking of an article prior to sending it to the journal for review. Please consult this Guide for Authors for further details of any item.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

- E-mail address
- Full postal address
- Phone numbers

All necessary files have been uploaded, and contain:

- Keywords
- All figure captions
- All tables (including title, description, footnotes)

Further considerations

- Manuscript has been 'spell-checked' and 'grammar-checked'
- References are in the correct format for this journal
- All references mentioned in the Reference list are cited in the text, and vice versa
- Permission has been obtained for use of copyrighted material from other sources (including the Web)
- Color figures are clearly marked as being intended for color reproduction on the Web (free of charge) and in print, or to be reproduced in color on the Web (free of charge) and in black-and-white in print
- If only color on the Web is required, black-and-white versions of the figures are also supplied for printing purposes

For any further information please visit our customer support site at <http://support.elsevier.com>.

Revised version of the manuscript

On the basis of the comments of the referees and editors, Authors may be asked to revise their manuscript. In order to facilitate the evaluation of the revisions by the referees and editors, upon revision, Authors are asked:

- to indicate all changes to the original manuscript by means of 'track changes'
- to add a letter for the referees, explaining how they dealt with all of the recommendations and questions from the referees.

Authors should submit their revised version no later than 2 months after they were informed about the decision that the manuscript needs revision. If no revised manuscript is received 2 months after the decision, the manuscript will be considered as rejected. If a second (or third) revision is necessary, the time is usually 1 month for re-submission.

AFTER ACCEPTANCE

Use of the Digital Object Identifier

The Digital Object Identifier (DOI) may be used to cite and link to electronic documents. The DOI consists of a unique alpha-numeric character string which is assigned to a document by the publisher upon the initial electronic publication. The assigned DOI never changes. Therefore, it is an ideal medium for citing a document, particularly 'Articles in press' because they have not yet received their full bibliographic information. Example of a correctly given DOI (in URL format; here an article in the journal *Health Policy*):

<http://dx.doi.org/10.1016/j.healthpol.2010.09.00>

When you use a DOI to create links to documents on the web, the DOIs are guaranteed never to change.

Online proof correction

Corresponding authors will receive an e-mail with a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors.

If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.

We will do everything possible to get your article published quickly and accurately - please upload all of your corrections within 48 hours. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility. Note that Elsevier may proceed with the publication of your article if no response is received.

AudioSlides

The journal encourages authors to create an AudioSlides presentation with their published article. AudioSlides are brief, webinar-style presentations that are shown next to the online article on ScienceDirect. This gives authors the opportunity to summarize their research in their own words and to help readers understand what the paper is about. More information and examples are available at <http://www.elsevier.com/audioslides>. Authors of this journal will automatically receive an invitation e-mail to create an AudioSlides presentation after acceptance of their paper.

Offprints

The corresponding author, at no cost, will be provided with a personalized link providing 50 days free access to the final published version of the article on ScienceDirect. This link can also be used for sharing via email and social networks. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's WebShop (<http://webshop.elsevier.com/myarticleservices/offprints>). Authors requiring printed copies of multiple articles may use Elsevier WebShop's 'Create Your Own Book' service to collate multiple articles within a single cover (<http://webshop.elsevier.com/myarticleservices/booklets>).

AUTHOR INQUIRIES

You can track your submitted article at http://help.elsevier.com/app/answers/detail/a_id/89/p/8045/.
You can track your accepted article at <http://www.elsevier.com/trackarticle>. You are also welcome to contact Customer Support via <http://support.elsevier.com>.

© Copyright 2014 Elsevier | <http://www.elsevier.com>